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WITNESS my hand this
Eleventh day of December 2003

J. Billingsley

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AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Therapeutic and diagnostic agents"

The invention is described in the following statement:

THERAPEUTIC AND DIAGNOSTIC AGENTS

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to therapeutic and diagnostic agents. More particularly, the present invention provides molecules having structural features characteristic of immunoregulatory signalling (IRS) molecules and which are expressed by cells of hematopoietic lineages such as, in particular, leukocytes. The molecules of the present invention find broad application *inter alia* as diagnostic markers for cells, targets for cell therapy and as validated drug targets in order to modulate the immune response and to treat, prevent and diagnose conditions associated with aberrant hematopoietic cell function or activity. The present invention extends to binding partners of the instant molecules such as, for example, antibodies, ligands, adaptor and other signalling associated molecules, agonists and antagonists and to methods of screening for same.

DESCRIPTION OF THE PRIOR ART

Bibliographic details of references provided in the subject specification are also listed at the end of the specification.

Reference to any prior art in this specification is not and should not be taken as an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in any country.

The increasing sophistication of recombinant DNA technology is greatly facilitating research and development in a range of biotechnology-related industries. The availability of therapeutic or prophylactic reagents which regulate or manipulate immune responses in the body is developing, based largely on the ability to clone and study molecules which are expressed by cells of the immune system. Cell-surface and secreted molecules are

particularly important expression products.

The Immunoregulatory Signalling (IRS) family is a group of cell surface molecules which regulate leukocyte function by delivering signals to the cells on which they are expressed. Members of the IRS family are typically either Immunoglobulin gene superfamily members or C-type lectins. Delivery of signals by these IRS molecules is through control of protein phosphorylation. Triggering IRS molecules typically associate with adaptor molecules that contain a cytoplasmic immuno tyrosine based activatory motif (ITAM) which interacts with SH2 domain-containing tyrosine kinases. To-date, a number of common adaptor molecules have been described; CD3ζ, FcεRγ, DAP12 and DAP10 (Wilson MJ, Lindquist JA, Trowsdale *J: Immunol Res 22*:21, 2000). These triggering molecules contain either an arginine or lysine residue in the transmembrane region and their expression on the cell surface requires co-expression of the correct adaptor molecule. Inhibitory IRS molecules have one or more tyrosine based inhibitory motif (ITIM) in their cytoplasmic domains which interacts with SH2 domain-containing tyrosine phosphatases.

The leukocyte receptor complex is a large complex of IRS encoding genes on human chromosome 19q13.4 that has been characterized (Wende *et al., Immunogenetics 51*: 703, 2000; Wende *et al., Mamm Genome 10*(2): 154, 1999; Wilson *et al., Methods Mol Biol 121*: 251, 2000; Wagtmann *et al., Current Biol 7*:615, 1997). The complex contains more than twenty genes belonging to the IRS family and includes the genes for the immunoglobulin like transcript (ILT) molecules, the killer Ig-like receptor (KIR) molecules and the natural cytotoxic receptor (NCR) molecule NKp46.

The CMRF-35A and CMRF-35H molecules are also IRS molecules (Clark *et al., Tissue Antigens 55:* 101-109, 2000; Clark *et al., Tissue Antigens 57:* 415-423, 2001; Green *et al., Int Immunol. 10*: 891-899, 1998) having, in the case of CMRF-35H, ITIM in the cytoplasmic region.

35A and 35H are expressed throughout hematopoiesis from the early bone marrow precursors by most leukocyte lineages involved in innate and adaptive immunity. Both

molecules are members of the Ig superfamily, each having a single V-like extracellular domain. They are most closely related to the Ig binding domains of the Fc receptor for polymeric IgA and IgM (Jackson *et al., Eur. J. Immunol. 22:* 1157-1163, 1992; Green *et al., Int. Immunol. 10:* 891-899, 1998P) but are also distantly related to the TREM molecules (Bouchon *et al., J. Immunol. 164:* 4991-4995, 2000), NKp44 (Vitale *et al., J. Exp. Med. 187:* 2065-2072, 1998) and NKp46 (Pessino *et al., J. Exp. Med. 188:* 953-960, 1998).

Like other IRS molecules, CMRF-35A and CMRF-35H are emerging as molecules which will shed light on how immune cells monitor and respond to their environment. In accordance with the present invention, molecules related to CMRF-35A and CMR-35H have been identified as a family of CMRF-35A and CMRF-35H-like molecules, which are expressed on defined cells and which are encoded by members of a gene family. The term "35-LM" is used in this specification to encompass CMRF-35-like molecules and includes CMRF-35A, CMRF-35H and all other closely related molecules.

SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Nucleotide and amino acid sequences are referred to by a sequence identifier number (SEQ ID NO:). The SEQ ID NOs: correspond numerically to the sequence identifiers <400>1 (SEQ ID NO:1), <400>2 (SEQ ID NO:2), etc. A summary of the sequence identifiers is provided in Table 2. A sequence listing is provided at the end of the specification.

In accordance with the present invention, a family of closely linked genes on human chromosome 17 has been identified which comprises members encoding polypeptides which are structurally related to the leukocyte surface glycoproteins CMRF-35A and CMRF-35H.

For comparative purposes, the nucleotide and amino acid sequences of human CMRF-35A are set forth in SEQ ID NOs:1 and 2, respectively and the nucleotide and amino acid sequences of human CMRF-35H are set forth in SEQ ID NOs:3 and 4, respectively. In this context, reference to "h" is a reference to a moleclue derived from human species; similarly, the prefix "m" is a reference to a molecule derived from mice. The term "35-LM"is used to encompass CMRF-35A, CMRF-35H and related molecules. Table 1 provides a summary of 35-LMs of the present invention.

In one embodiment the present invention provides a nucleic acid molecule or a derivative or homolog thereof corresponding to a gene family which is located on human chromosome 17q22-24 or the equivalent region in other species (e.g. chromosome 11 in mice). The nucleic acid molecules of the present invention, in a further embodiment, encode a polypeptide having one or more of the identifying characteristics of 35A or 35H selected from the following:

(i) sequence similarity to an Ig binding domain of CMRF-35A or CMRF-35H;

(ii) sequence similarity to a cytoplasmic ITIM motif; or

(iii) expression of polypeptide *in vivo* requires binding to an adaptor molecule comprising an ITAM motif.

The polypeptides may be expressed on the surface of defined populations of hematopoietic cells or may be excreted or be in soluble form.

A homolog includes a nucleic acid molecule comprising a nucleotide sequences having at least 40% similarity or higher to SEQ ID NO:1 (hCMRF-35A) or SEQ ID NO:3 (hCMRF-35H) SEQ ID NO:5 (h35-L1), SEQ ID NO:7 (h35-L2), SEQ ID NO:9 (h35-L3), SEQ ID NO:11 (h35-L4) or SEQ ID NO:13 (h35-L5) or SEQ ID NO:15 (m35a) or SEQ ID NO:17 (m35c) or SEQ ID NO:19 (m35d) or SEQ ID NO:21 (m35f) or SEQ ID NO:23 (m35a) or SEQ ID NO:25 (m35g), or to its complementary form or which is capable of hybridizing to SEQ ID NO:1 or SEQ ID NO:3 or SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11 or SEQ ID NO:13 or SEQ ID NO:15 or SEQ ID NO:17 or SEQ ID NO:19 or SEQ ID NO:21 or SEQ ID NO:23 or SEQ ID NO:25, or its complementary form under low stringency conditions.

In another embodiment, the present invention provides an isolated or recombinant polypeptide derived from the present nucleic acid molecules. In a preferred embodiment, the polypeptides are expressed on the surface of defined populations of hematopoietic cells and conveniently provide cell surface markers for these cell types. In one embodiment, the 35-LMs are expressed on the surface of leukocytes and are capable of influencing the ability of the leukocyte to respond to its environment. Specifically, expression of the 35-LMs influences the ability of the cells to proliferate, differentiate, activate, express cytokines, perform effector functions or undergo apoptosis.

In yet another embodiment, the polypeptide comprises a sequence of amino acids selected from those set forth in SEQ ID NO:2 (hCMRF-35A) or SEQ ID NO:4 (hCMRF-35H) or SEQ ID NO: 6 (h35-L1) or SEQ ID NO:8 (h35-L2)or SEQ ID NO:10 (h35-L3) or SEQ ID NO:12 (h35-L4)or SEQ ID NO:14 (h35-L5) or SEQ ID NO:16 (m35a) or SEQ ID NO:18 (m35c) or SEQ ID NO:20 (m35d) or SEQ ID NO:22 (m35f) or SEQ ID NO:24 (m35h) or SEQ ID NO:26 (m35g) or an amino acid sequence having at least 20% similarity to all or part of any one of the listed sequences. In another embodiment the instant polypeptide is encoded by a nucleotides sequence set forth in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25 or by a nucleotide sequence having at least about 20% similarity thereto or a nucleotide sequence capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 or SEQ ID NO:25 or its complementary form under low stringency conditions. Binding partners may be used to activate or inhibit the immune system.

In another embodiment, binding partners including soluble forms of the instant polypeptides, antibodies, ligands, agonist and antagonists are usefully developed as diagnostic, therapeutic or prophylactic agents. As targets for cell therapy, the nucleic acid and polypeptide molecules of the present invention provide targets in screens for specific binding partners. Binding partners are contemplated for use in the treatment, prevention or diagnosis of conditions associated with aberrant cellular immunity or altered immune cell function or activity, as is found in cancer, autoimmune conditions, infections, immunosuppression and inflammation, among others.

TABLE 1

Nomenclature for CMRF-35 family of molecule

FAMILY NAME	NOMENCLATURE	MOUSE ORTHOLOG
35-LM	CMRF-35A	m35h
	CMRF-35H	m35c
	35-L1	m35f
	35-L2	m35d
	35-L3	DIgR1
	35-L4	m35e
	35-L5	m35g DIgR2 m35a

A summary of sequence identifiers used throughout the subject specification is provided in Table 2.

TABLE 2

Summary of Sequence Identifiers

SEQUENCE ID NO:	DESCRIPTION
1	Nucleotide sequence of hCMRF-35A
2	Amino acid sequence of hCMRF-35A
3	Nucleotide sequence of hCMRF-35H
4	Amino acid sequence of hCMRF-35H
5	Nucleotide sequence of h35-L1
6	Amino acid sequence of h35-L1
7	Nucleotide sequence of h35-L2
8	Amino acid sequence of h35-L2
9	Nucleotide sequence of h35-L3
10	Amino acid sequence of h35-L3
11	Nucleotide sequence of h35-L4
12	Amino acid sequence of h35-L4
13	Nucleotide sequence of h35-L5
14	Amino acid sequence of h35-L5
15	Nucleotide sequence of m35-a
16	Amino acid sequence of m35-a
17	Nucleotide sequence of m35-c
18	Amino acid sequence of m35-c
19	Nucleotide sequence of m35-d
20	Amino acid sequence of m35-d
21	Nucleotide sequence of m35-f
22	Amino acid sequence of m35-f
23	Nucleotide sequence of m35-h
24	Amino acid sequence of m35-h

SEQUENCE ID NO:	DESCRIPTION
25	Nucleotide sequence of m35-g
26	Amino acid sequence of m35-g
27	Amino acid sequence of m35-e (Ig domain)

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a representation of an alignment of the nucleic acid sequences of 35-LMs.

Figure 2 is a representation of an alignment of predicted amino acid sequences of 35-LMs.

Figure 3 is a diagrammatic representation showing the expression analysis of the h35-LMs on cell lines and freshly purified hemopoietic populations.

Figure 4 is a photographic representation showing the expression of AW8 (also called 35-L3) RNA assayed by RT-PCR. Filters are probed with a specific AW8 oligonucleotide. M; marker, 1; B cells, 2; NK cells, 3; granulocytes, 4; monocytes, 5; lin-ve dendritic cells, 6; monocyte derived DC, 7; activated monocyte derived DC, 8; T cells, 9; negative control.

Figure 5 is a representation of an alignment of the nucleic acid sequences of m35-LMs.

Figure 6 is a representation of an alignment of the predicted amino acid sequences of the mouse.

Figure 7 is a diagrammatic representation showing the expression analysis of the m35-LMs on cell lines and freshly purified hematopoietic populations.

Figure 8 is a diagrammatic representation showing the structure the three molecule types in the 35-LM family:-

Type I	=	Inhibitory
Type II	=	E residue in the transmembrane domain
Type III	=	K residue in the transmembrane domain

Figure 9 is a photographic representation showing family expression in various BALB/c tissue, cell lines and sorted spleen cell populations. Pictures show gel photos (dark

background) and Southerns (light background). **(A) to (G)** show m35a, m35c, m35e, m35f, m35g, m35h and DIgR1 expression. Expected fragment size is indicated on the right hand side. **(H)** RT-PCR using mouse GAPDH primers on a selection of cDNA samples with and without (c, control) reverse transcriptase. Integrity of all cDNA samples was confirmed before use for expression analysis. (Thy, thymus; LN, lymph node; BM, bone marrow; Kid, kidney; Hea, heart; Mono, monocytes; Gran; granulocytes).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides members of a new family of immunoregulatory signalling-like molecules encoded by nucleic acid molecules which correspond to a gene family located on human chromosome 17q22-24 or the equivalent region in other species. These molecules are referred to as 35-LMs for "CMRF-35-like molecules".

Accordingly, one aspect of the present invention provides an isolated or recombinant nucleic acid molecule, or a derivative or homolog thereof, corresponding to a gene family which is located on human chromosome 17q22-24 or the equivalent region in other species. The equivalent region in mouse species, for example, is on chromosome 11.

The nucleic acid molecule may be isolated or derived from any suitable animal such as humans, primates, livestock animals (e.g. horses, cows, sheep, donkeys, pigs), laboratory test animals (e.g. mice, rats, rabbits, hamsters, guinea pigs), companion animals (e.g. dogs, cats), or captive wild animals (e.g. deer, foxes, kangaroo). Various databases are now available which compare chromosomal regions of synteny between two species, see for example the Seldin/Debry human/mouse homology map available through OPIM at http://www3.ncbi.lmn.hih.gov/omim, among others.

As used herein, the term "derived from" means that a particular element or group of elements has originated from the source described, but has not necessarily been obtained directly from the specified source.

The terms "nucleic acid molecule", "genetic sequence", "sequence of nucleotides" include RNA, cDNA, genomic DNA, synthetic forms and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e.g. methyl phosphonates, phosphotriesters, phosphoamidates,

carbamates, etc.), charged linkages (e.g. phosphorothioates, phosphorodithioates, etc.), pendent moieties (e.g. polypeptides), intercalators (e.g. acridine, psoralen, etc.), chelators, alkylators and modified linkages (e.g. α-anomeric nucleic acids, etc.). Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence *via* hydrogen binding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule. The nucleic acid molecules of the present invention may be in single, double stranded form and other multiple forms thereof.

Reference herein to a nucleic acid molecule includes reference to a "gene".

The present nucleic acid molecules correspond to a gene family and may be independently or co-ordinately expressed therefrom. The nucleic acid molecules may be full length genes or they may be parts thereof.

The term "gene" is used in its broadest sense and includes cDNA corresponding to the exons of a gene. Reference herein to a "gene" is also taken to include:-

(i) a classical genomic gene consisting of transcriptional and/or translational regulatory sequences and/or a coding region and/or non-translated sequences (i.e. introns, 5'- and 3'- untranslated sequences); or

(ii) mRNA or cDNA corresponding to the coding regions (i.e. exons) and 5'- and 3'- untranslated sequences of the gene.

Reference to a "part " of a nucleic acid molecule according the present invention includes fragments of longer molecules defined as having a minimal size of at least about 10 nucleotides or preferably about 13 nucleotides or more preferably 17, 18, 19 or 20 nucleotides. There is no maximal size but a size of about 200 contiguous nucleotides is a useful maximum. Such parts may be useful as probes or primers. Alternatively such molecules may encode a polypeptide such as a soluble protein lacking a cytoplasmic or

transmembrane domain. Accordingly, this definition includes all sizes in the range of 10-200 nucleotides as well as greater than 200 nucleotides. Thus, this definition includes nucleic acids of 12, 15, 17, 18, 19, 20, 25, 40, 60, 80, 100, 200, 300, 400, 500, 1000 or 1500 nucleotides or nucleic acids having any number of nucleotides within these values (e.g. 13, 16, 23, 30, 28, 50, 72, 121, etc. nucleotides) or nucleic acids having more than 1500 nucleotides or any number of nucleotides between 1500 and the number shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 or SEQ ID NO:25.

Members of the 35-LM family may be identified or cloned by any of a wide range of strategies including interaction of the polypeptides of the family with specific antibodies, homology cloning, *in silico* mining, through EST database or through further mapping and cloning procedures in relation to the 35-LM genomic complex. A number of strategies also exist for cloning full length cDNAs from the short sequences generated including screening cDNA libraries and 5' and 3' RACE strategies. General teaching on manipulating and cloning nucleic acid molecules may be found in Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, 3rd Edition, 2001).

The isolated or recombinant nucleic acid molecule of the present invention may be deployed in appropriate vectors and cells for sequencing, cloning, expression or for administration to a cell, as described in standard laboratory manuals such as Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons Inc, 1994-1998.

Homologs of the instant nucleic acid sequences include orthologous gene sequences from different species which are related by common phylogenic descent and gene sequences from other species which are similar to the instant nucleic acid molecules as a result of, for example, convergent evolution, wherein the homologs are functionally and structurally related to the instant nucleic acid sequences and are consequently readily identified and/or isolated by hybridization based methods or by sequence comparison

with available genetic databases. A homolog includes a nucleic acid molecule comprising a nucleotide sequences having at least 40% similarity or higher to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 or SEQ ID NO:25, or to its complementary form or which is capable of hybridizing to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23 or SEQ ID NO:25, or its complementary form under low stringency conditions.

The term "similarity" as used herein includes exact identity between compared sequences at the nucleotide or corresponding amino acid level. Where there is non-identity at the nucleotide level, "similarity" includes differences between sequences which result in different amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. Where there is non-identity at the amino acid level, "similarity" includes amino acids that are nevertheless related to each other at the structural, functional, biochemical and/or conformational levels. In a particularly preferred embodiment, nucleotide and sequence comparisons are made at the level of identity rather than similarity.

Terms used to describe sequence relationships between two or more polynucleotides or polypeptides include "reference sequence", "comparison window", "sequence similarity", "sequence identity", "percentage of sequence similarity", "percentage of sequence identity", "substantially similar" and "substantial identity". A "reference sequence" is at least 12 but frequently 15 to 18 and often at least 25 or above, such as 30 monomer units, inclusive of nucleotides and amino acid residues, in length. Because two polynucleotides may each comprise (1) a sequence (i.e. only a portion of the complete polynucleotide sequence) that is similar between the two polynucleotides, and (2) a sequence that is divergent between the two polynucleotides, sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a "comparison window" to identify and compare local regions of

sequence similarity. A "comparison window" refers to a conceptual segment of typically 12 contiguous residues that is compared to a reference sequence. The comparison window may comprise additions or deletions (i.e. gaps) of about 20% or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by computerized implementations of algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Drive Madison, WI, USA) or by inspection and the best alignment (i.e. resulting in the highest percentage homology over the comparison window) generated by any of the various methods selected. Reference also may be made to the BLAST family of programs as, for example, disclosed by Altschul *et al.*, *Nucl. Acids Res. 25:* 3389. 1997. A detailed discussion of sequence analysis can be found in Unit 19.3 of Ausubel *et al.*, 1994-1998, *supra*).

The terms "sequence similarity" and "sequence identity" as used herein refers to the extent that sequences are identical or functionally or structurally similar on a nucleotide-by-nucleotide basis or an amino acid-by-amino acid basis over a window of comparison. Thus, a "percentage of sequence identity", for example, is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (e.g. A, T, C, G, I, U) or the identical amino acid residue (e.g. Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys and Met) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (i.e., the window size), and multiplying the result by 100 to yield the percentage of sequence identity. For the purposes of the present invention, "sequence identity" will be understood to mean the "match percentage" calculated by the DNASIS computer program (Version 2.5 for windows; available from Hitachi Software engineering Co., Ltd., South San Francisco, California, USA) using standard defaults as used in the reference manual accompanying the software. Similar comments apply in relation to sequence similarity.

Preferably, the percentage similarity between a particular sequence and a reference sequence (nucleotide or amino acid) is at least about 30% or at least about 40% or at least about 50% or at least about 65% or at least about 70% or at least about 80% or at least about 90% or at least about 95% or above such as at least about 96%, 97%, 98%, 99% or greater. A percentage identity of approximately 30-32% is particularly preferred.

Similarity at the nucleic acid level may be assessed in assays exploiting different stringency of hybridization conditions as is well known in the art and is, for example, described in Ausubel *et al., supra,* 1994-1998.

Reference herein to stringent hybridization conditions preferably means conditions which permit selective hybridization or annealing between molecules which are substantially similar. The hybridization temperature composition and ionic strength of the hybridization solution which meet this criteria will vary depending upon a number of well characterized factors such as length, degree of complementarity and GC content. For longer sequences it is generally possible to calculate the expected melting point of duplex nucleic acid sequences under various conditions. Hybridization may be to all or part of the instant polynucleotides with the minimum length being sufficient to provide specificity.

Low stringency hybridization conditions includes and encompasses from at least about 0 to at least about 15% v/v formamide and from at least about 1 M to at least about 2 M salt for hybridization, and at least about 1 M to at least about 2 M salt for washing conditions. Generally, low stringency is at from about 25-30°C to about 42°C. The temperature may be altered and higher temperatures used to replace formamide and/or to give alternative stringency conditions.

Medium stringency includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5 M to at least about 0.9 M salt for hybridization, and at least about 0.5 M to at least about 0.9 M salt for washing conditions. High stringency includes and encompasses from at least about 31% v/v to at least about

50% v/v formamide and from at least about 0.01 M to at least about 0.15 M salt for hybridization, and at least about 0.01 M to at least about 0.15 M salt for washing conditions. In general, washing is carried out $T_m = 69.3 + 0.41$ (G+C%). However, the T_m of a duplex DNA decreases by 1°C with every increase of 1% in the number of mismatch base pairs (Bonner and Laskey, *Eur. J. Biochem. 46:* 83, 1974). Formamide is optional in these hybridization conditions. Accordingly, particularly preferred levels of stringency are defined as follows: low stringency is 6 x SSC buffer, 0.1% w/v SDS at 25-42°C; a moderate stringency is 2 x SSC buffer, 0.1% w/v SDS at a temperature in the range 20°C to 65°C; high stringency is 0.1 x SSC buffer, 0.1% w/v SDS at a temperature of at least 65°C.

As used herein, an "isolated" or "substantially pure" nucleic acid molecule (e.g. an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native sequence or protein, e.g. ribosomes, polymerases and many other genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.

The present invention further provides recombinant nucleic acids including a recombinant construct comprising all or a part of the present gene family. The recombinant construct may be capable of replicating autonomously in a host cell. Alternatively, the recombinant construct may become integrated into the chromosonal DNA of the host cell. Such a recombinant polynucleotide comprises a polynucleotide of genomic, cDNA, semi-synthetic or synthetic origin which, by virtue of its origin or manipulation: (i) is not associated with all or a portion of a polynucleotide with which it is associated in nature; (ii) is linked to a polynucleotide other than that to which it is linked in nature; or (iii) does not occur in nature. Where nucleic acids according to the invention include RNA, reference to the sequence shown should be construed as reference to the RNA equivalent with U substituted for T. A "recombinant construct" includes an expression construct whereby the nucleotide sequence is expressed to form mRNA. The recombinant construct

may be RNA or DNA.

Accordingly, recombinant nucleic acids comprising sequences otherwise not naturally occurring are provided by the present invention. Although the wild-type sequence may be employed, it will often be altered, e.g. by deletion, substitution or insertion of one or more nucleotides.

cDNA or genomic libraries of various types may be screened as natural sources of the nucleic acids of the present invention or such nucleic acids may be provided by amplification of sequences resident in genomic DNA or other natural sources, e.g. by PCR. The choice of cDNA libraries normally corresponds to a tissue source which is abundant in mRNA for the desired protein. Phage or plasmid libraries are normally preferred but other types of libraries may be used. Clones of a library are spread onto plates, transferred to a substrate for screening, denatured and probed for the presence of desired sequences.

The nucleic acid molecules of the present invention may be produced by replication in a suitable host cell. Natural or synthetic polynucleotide fragments coding for a desired fragment will be incorporated into recombinant polynucleotide constructs, usually DNA constructs, capable of introduction into and replication in a prokaryotic or eukaryotic cell. Usually the polynucleotide constructs will be suitable for replication in a unicellular host, such as yeast or bacteria, but may also be intended for introduction into (with or without integration within the genome) cultured mammalian or other eukaryotic cell lines. The purification of nucleic acids produced by the methods of the present invention are described, e.g. in Sambrook *et al., Molecular Cloning: A Laboratory Manual,* 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1989 or Ausubel *et al.,*"Current Protocols in Molecular Biology" John Wiley & Sons Inc, 1992.

The polynucleotides of the present invention may also be produced by chemical synthesis, e.g. by the phosphoramidite method described by Beaucage and Carruthers (*Tetra Letts 22:* 1859-1862, 1981) or the triester method according to Matteucci and Caruthers (*J. Am. Chem. Soc. 103:* 3185, 1981) and may be performed on commercial, automated

oligonucleotide synthesizers. A double-stranded fragment may be obtained from the single-stranded product of chemical synthesis either by synthesizing the complementary strand and annealing the strands together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

An appropriate promoter and other necessary vector sequences, including selectable markers, will be selected so as to be functional in the host and may include, when appropriate, those naturally associated with the 35-LM gene family. Examples of workable combinations of cell lines and expression vectors are described in Sambrook *et al.*, 1989, *supra* or Ausubel *et al.*, 1992, *supra*. Many useful vectors are known in the art and may be obtained from such vectors as Stratagene, New England Biolabs, Promega Biotech and others. Promoters such as the trp, lac and phage promoters, tRNA promoters and glycolytic enzyme promoters may be used in prokaryotic hosts. Useful yeast promoters include promoter regions for metallothionein, 3-phosphoglycerate kinase or other glycolytic enzymes such as enolase or glyceraldehyde-3-phosphate dehydrogenase, enzymes responsible for maltose and galactose utilization and others. Vectors and promoters suitable for use in yeast expression are further described in European Patent Publication No. 0 073 675. Appropriate non-native mammalian promoters might include the early and late promoters from SV40 (Fiers *et al., Nature 273:* 113-120, 1978) or promoters derived from murine molony leukemia virus, mouse tumor virus, avian sarcoma viruses, adenovirus II, bovine papilloma virus or polyoma. The CMV promoter is particularly useful in expressing 35-LM genes or cDNA. Insect promoters may be derived from baculovirus. In addition, the construct may be joined to an amplifiable gene (e.g. DHFR) so that multiple copies of the gene may be made. For appropriate enhancer and other expression control sequences, see also *Enhancers and Eukaryotic Gene Expression*, Cold Spring Harbor Press, Cold Spring Harbour, New York (1983). See also, e.g. U.S. Patent No. 5,691,198.

The vectors containing the nucleic acids of interest can be transcribed *in vitro* and the resulting RNA introduced into the host cell by well-known methods, e.g. by injection (see Kubo *et al., FEBS Lett. 241:* 119, 1988), or the vectors can be introduced directly into host

cells by methods well known in the art, which vary depending on the type of cellular host, including electroporation; transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; infection (where the vector is an infectious agent, such as a retroviral genome); and other methods. See generally, Sambrook *et al.* (1989) *supra* and Ausubel *et al.* (1992) *supra*. The introduction of the polynucleotides into the host cell by any method known in the art, including, *inter alia,* those described above, will be referred to herein as "transformation". The cells into which have been introduced nucleic acids described above are meant to also include the progeny of such cells.

Large quantities of the nucleic acids and polypeptides (see below) of the present invention may be prepared by expressing the *35-LM* nucleic acids or parts thereof in vectors or other expression vehicles in compatible prokaryotic or eukaryotic host cells. The most commonly used prokaryotic hosts are strains of *E. coli,* although other prokaryotes, such as *Bacillus subtilis* or *Pseudomonas* may also be used.

Mammalian or other eukaryotic host cells, such as those of yeast, filamentous fungi, plant, insect or amphibian or avian species, may also be useful for production of the proteins of the present invention. Propagation of mammalian cells in culture is *per se* well known. See, Jakoby and Pastan (eds.), *Cell Culture. Methods in Enzymology*, Vol. 58, Academic Press, Inc., Harcour Brace Jovanovich, New York, 1979. Examples of commonly used mammalian host cell lines are VERO and HeLa cells, Chinese hamster ovary (CHO) cells, and WI38, BHK and COS cell lines. The Jurkat T-cell line is particularly useful in the practice of this aspect of the present invention. An example of a commonly used insect cell line is SF9. However, it will be appreciated by the skilled practitioner that other cell lines may be appropriate, e.g. to provide higher expression, desirable glycosylation patterns or other features.

Clones are selected by using markers depending on the mode of the vector construction. The marker may be on the same or a different DNA molecule, preferably the same DNA molecule. In prokaryotic hosts, the transformant may be selected, e.g. by resistance to

ampicillin, tetracycline or other antibiotics. Production of a particular product based on temperature sensitivity may also serve as an appropriate marker.

Prokaryotic or eukaryotic cells transformed with the polynucleotides of the present invention will be useful not only for the production of the nucleic acids and polypeptides of the present invention but also, for example, in studying the characteristics of a *35-LM* expression product such as a polypeptide, mRNA, intron and exon.

Antisense polynucleotide sequences are useful in modulating the expression of members of the gene family. Polynucleotide vectors, for example, containing all or a part of the present nucleic acid molecule may be placed under the control of a promoter in an antisense orientation and introduced into a cell. Expression of such an antisense construct within a cell will interfere with the target *35-LM* transcription or translation. Furthermore, co-suppression and mechanisms to induce RNAi may also be employed. Such techniques may be useful to selectively inhibit inhibitory 35-LMs in subjects with for example immunosuppression and may also be useful to inhibit triggering 35-LMs in subjects with for example inflammatory or autoimmune conditions. Selective inhibition may involve the use of cell or tissue or cell cycle stage specific promoters to regulate expression of the antisense molecules in certain cell types or tissues, or over particular time periods.

Another embodiment of the present invention contemplates an isolated or recombinant nucleic acid molecule corresponding to a gene family which is located on human chromosome 17q22-24 or the equivalent region in another species and comprising a sequence of nucleotides encoding or complementary to a sequence encoding a polypeptide or a nucleotide sequence capable of hybridizing thereto under low stringency conditions wherein said polypeptide exhibits one or more of the identifying characteristics of hCMRF-35A or hCMRF-35H and wherein said polypeptide is expressed on the surface of defined populations of hematopoietic cells.

In a preferred embodiment, the polypeptide comprises a sequence of amino acids selected from those set forth in SEQ ID NO: 6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12,

SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, or SEQ ID NO:26 or an amino acid sequence having at least 20% similarity to all or part of any one of the listed sequences.

Particularly preferred nucleic acid molecules comprise nucleotide sequences substantially as set forth in SEQ ID NO:5 (h35-L1), SEQ ID NO:7 (h35-L2), SEQ ID NO:9 (h35-L3), SEQ ID NO:11 (h35-L4), SEQ ID NO:13 (h35-L5), SEQ ID NO:15 (m35-a), SEQ ID NO:17 (m35-c), SEQ ID NO:19 (m35-d), SEQ ID NO:21 (m35-f), SEQ ID NO:23 (m35-h), SEQ ID NO:25 (m35-g), or a nucleotide sequence having at least about 15% similarity to all or a part of the sequences or a nucleotide sequence which hybridizes to any of these medium stringency conditions.

The term "polypeptide" refers to a polymer of amino acids and its equivalent and does not refer to a specific length of the product, thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. This term also does not exclude modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like. Included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), polypeptides with substituted linkages as well as other modifications known in the art, both naturally and non-naturally occurring. Ordinarily, such polypeptides will be at least about 20% similar to the wild-type members of the 35-LM gene family, preferably in excess of 30% or 40% or 60% or 90% or 95%. Also included are proteins encoding by DNAs which hybridize under high or low stringency conditions to *35-LM* nucleic acids and closely related polypeptides or proteins retrieved by, for example, antibodies to the 35-LM family member.

The polypeptide molecules may be in isolated and purified form, free or substantially free of material with which it is naturally associated. The polypeptide may, if produced by expression in a prokaryotic cell or produced synthetically, lack native post-translational processing, such as glycosylation. The present invention is also directed to polypeptides which are sequence variants, alleles or derivatives of the 35-LM polypeptides.

Substitutional variants typically contain the exchange of one amino acid for another at one or more sites within the protein and may be designed to modulate one or more properties of the polypeptide such as stability against proteolytic cleavage without the loss of other functions or properties. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues involved. Preferred substitutions are ones which are conservative, that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and tyrosine, phenylalanine.

Certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, epitope-binding regions of antibodies or binding sites on substrate molecules or binding sites on proteins interacting with the 35-LM polypeptide. The interactive capacity and nature of a protein may define that protein's biological functional activity, and certain amino acid substitutions can be made in a protein sequence or its underlying DNA coding sequence and nevertheless obtain a protein with like properties. In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydrophobic amino acid index in conferring interactive biological function on a protein is generally understood in the art (Kyte and Doolittle, *J. Mol. Biol. 157:* 105-132, 1982). Alternatively, the substitution of like amino acids can be made effectively on the basis of hydrophilicity. The importance of hydrophilicity in conferring interactive biological function of a protein is generally understood in the art (U.S. Patent No. 4,554,101). The use of the hydrophobic index or hydrophilicity in designing polypeptides is further discussed in U.S. Patent No. 5,691,198.

The length of the polypeptide sequences compared for homology will generally be at least about 16 amino acids, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues and preferably more than about 35 residues.

The present invention further contemplates chemical analogs of a 35-LM polypeptide.

Analogues contemplated herein include but are not limited to modification to side chains, incorporating of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogs.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with $NaBH_4$; amidination with methylacetimidate; acetylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with $NaBH_4$.

The guanidine group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea formation followed by subsequent derivitization, for example, to a corresponding amide.

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acid, contemplated herein is shown in Table 3.

TABLE 3

Codes for non-conventional amino acids

Non-conventional amino acid	Code	Non-conventional amino acid	Code
α-aminobutyric acid	Abu	L-N-methylalanine	Nmala
α-amino-α-methylbutyrate	Mgabu	L-N-methylarginine	Nmarg
aminocyclopropane-	Cpro	L-N-methylasparagine	Nmasn
carboxylate		L-N-methylaspartic acid	Nmasp
aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
aminonorbornyl-	Norb	L-N-methylglutamine	Nmgln
carboxylate		L-N-methylglutamic acid	Nmglu
cyclohexylalanine	Chexa	L-Nmethylhistidine	Nmhis
cyclopentylalanine	Cpen	L-N-methylisolleucine	Nmile
D-alanine	Dal	L-N-methylleucine	Nmleu
D-arginine	Darg	L-N-methyllysine	Nmlys
D-aspartic acid	Dasp	L-N-methylmethionine	Nmmet
D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
D-isoleucine	Dile	L-N-methylproline	Nmpro
D-leucine	Dleu	L-N-methylserine	Nmser
D-lysine	Dlys	L-N-methylthreonine	Nmthr
D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
D-phenylalanine	Dphe	L-N-methylvaline	Nmval
D-proline	Dpro	L-N-methylethylglycine	Nmetg
D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug

D-threonine	Dthr	L-norleucine	Nle
D-tryptophan	Dtrp	L-norvaline	Nva
D-tyrosine	Dtyr	α-methyl-aminoisobutyrate	Maib
D-valine	Dval	α-methyl-γ-aminobutyrate	Mgabu
D-α-methylalanine	Dmala	α-methylcyclohexylalanine	Mchexa
D-α-methylarginine	Dmarg	α-methylcylcopentylalanine	Mcpen
D-α-methylasparagine	Dmasn	α-methyl-α-napthylalanine	Manap
D-α-methylaspartate	Dmasp	α-methylpenicillamine	Mpen
D-α-methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
D-α-methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
D-α-methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
D-α-methylisoleucine	Dmile	N-amino-α-methylbutyrate	Nmaabu
D-α-methylleucine	Dmleu	α-napthylalanine	Anap
D-α-methyllysine	Dmlys	N-benzylglycine	Nphe
D-α-methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
D-α-methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
D-α-methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
D-α-methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
D-α-methylserine	Dmser	N-cyclobutylglycine	Ncbut
D-α-methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
D-α-methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
D-α-methyltyrosine	Dmty	N-cyclodecylglycine	Ncdec
D-α-methylvaline	Dmval	N-cylcododecylglycine	Ncdod
D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr

D-N-methylhistidine	Dnmhis	N-(hydroxyethyl))glycine	Nser
D-N-methylisoleucine	Dnmile	N-(imidazolylethyl))glycine	Nhis
D-N-methylleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp
D-N-methyllysine	Dnmlys	N-methyl-γ-aminobutyrate	Nmgabu
N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpen
N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
D-N-methyltyrosine	Dnmtyr	N-methyla-napthylalanine	Nmanap
D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
γ-aminobutyric acid	Gabu	N-(*p*-hydroxyphenyl)glycine	Nhtyr
L-*t*-butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
L-ethylglycine	Etg	penicillamine	Pen
L-homophenylalanine	Hphe	L-α-methylalanine	Mala
L-α-methylarginine	Marg	L-α-methylasparagine	Masn
L-α-methylaspartate	Masp	L-α-methyl-*t*-butylglycine	Mtbug
L-α-methylcysteine	Mcys	L-methylethylglycine	Metg
L-α-methylglutamine	Mgln	L-α-methylglutamate	Mglu
L-α-methylhistidine	Mhis	L-α-methylhomophenylalanine	Mhphe
L-α-methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
L-α-methylleucine	Mleu	L-α-methyllysine	Mlys
L-α-methylmethionine	Mmet	L-α-methylnorleucine	Mnle
L-α-methylnorvaline	Mnva	L-α-methylornithine	Morn
L-α-methylphenylalanine	Mphe	L-α-methylproline	Mpro
L-α-methylserine	Mser	L-α-methylthreonine	Mthr
L-α-methyltryptophan	Mtrp	L-α-methyltyrosine	Mtyr
L-α-methylvaline	Mval	L-N-methylhomophenylalanine	Nmhphe

N-(N-(2,2-diphenylethyl) carbamylmethyl)glycine	Nnbhm	N-(N-(3,3-diphenylpropyl) carbamylmethyl)glycine	Nnbhe
1-carboxy-1-(2,2-diphenyl-ethylamino)cyclopropane	Nmbc		

Crosslinkers can be used, for example, to stabilize 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with n=1 to n=6, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety such as maleimido or dithio moiety (SH) or carbodiimide (COOH). In addition, peptides can be conformationally constrained by, for example, incorporation of C_α and N_α-methylamino acids, introduction of double bonds between C_α and C_β atoms of amino acids and the formation of cyclic peptides or analogues by introducing covalent bonds such as forming an amide bond between the N and C termini, between two side chains or between a side chain and the N or C terminus.

The term "peptide mimetic" or "mimetic" is intended to refer to a substance which has the essential biological activity of the 35-LM family member polypeptide. A peptide mimetic may be a peptide-containing molecule that mimics elements of protein secondary structure. The underlying rationale behind the use of peptide mimetics is that the peptide backbone of proteins exists chiefly to orient amino acid side chains in such a way as to facilitate molecular interactions such as those of antibody and antigen, enzyme and substrate or scaffolding proteins. A peptide mimetic is designed to permit molecular interactions similar to the natural molecule. A mimetic may not be a peptide at all, but it will retain the essential biological activity of a natural 35-LM polypeptide.

The present invention is particularly useful, therefore, for screening compounds by using one or more 35-LM family member polypeptide or binding fragment thereof in any of a variety of drug screening techniques, such as those described herein and in International Publication No. WO 97/02048.

The 35-LM family member polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, or borne on a cell surface. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant polynucleotides expressing the polypeptide or fragment, preferably in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between a polypeptide or fragment and the agent being tested, or examine the degree to which the formation of a complex between a 35-LM polypeptide or a part thereof and a specific antibody is aided or interfered with by the agent being tested.

Polyclonal antibodies may conveniently be used, however, the use of monoclonal antibodies in an immunoassay is particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation of hybridoma cell lines for monoclonal antibody production is derived by fusing an immortal cell line and lymphocytes sensitized against the immunogenic preparation (i.e. comprising 35-LM polypeptide) or can be done by techniques which are well known to those who are skilled in the art. (See, for example, Douillard and Hoffman, Basic Facts about Hybridomas, in *Compendium of Immunology* Vol. II, ed. by Schwartz, 1981; Kohler and Milstein, *Nature 256:* 495-499, 1975; Kohler and Milstein, *European Journal of Immunology 6:* 511-519, 1976). Single chain antibodies or transgenic mice expressing humanized antibodies or other recognition proteins may also be used. Useful proteins in this regard include diabodies, peptide mimetics and antibody fragments such as scFv fragments and Fab fragments.

Monoclonal antibodies which bind specifically to members of the 35-LM family provide a convenient method for detecting and targeting the cells which express one or more 35-LM. For detecting one or more cells expressing particular 35-LMs either alone or in conjunction with other cell surface molecules, an large number of assays are available. For example, populations of cells may be routinely assessed for their 35-LM polypeptide cell surface markers using identifiable polypeptide specific binding partners such as primary antibodies

to cell surface markers and secondary antibodies labeled with detectable markers. Antibodies may further differentiate between allelic or altered forms of 35-LM polypeptides. The presence of members of the 35-LM members may be accomplished in a number of ways such as by Western blotting and ELISA procedures. A wide range of immunoassay techniques are available as can be seen by reference to U.S. Patent Nos. 4,016,043, 4,424,279 and 4,018,653. These include both single-site and two-site or "sandwich" assays of the non-competitive types, as well as in the traditional competitive binding assays. These assays also include direct binding of a labeled antibody to a target. Monoclonal antibodies may be used as agonists or antagonists of 35-LM polypeptide activity. They may also be formulated as a composition suitable for administation to an individual in a method of treatment or prophylaxis.

The antibodies of the present invention are useful in a range of other methodologies including flow cytometry, which typically detects optical parameters. For example, a flow cytometer may be used to determine forward scatter (which is a measure of size of a carrier), side scatter (which is sensitive to refractive index and size of a particle [see Shapiro, *"Practical flow cytometry"*, 3rd ed. Brisbane, Wiley-Liss, 1995]) and fluorescent emission.

As is known in the art, flow cytometry is a high throughput technique which involves rapidly analyzing the physical and chemical characteristics of cells or other particles as they pass through the path of one or more laser beams while suspended in a fluid stream. As each cell or particle intercepts the laser beam, the scattered light and fluorescent light emitted by each cell or particle is detected and recorded using any suitable tracking algorithm.

A modern flow cytometer is able to perform these tasks up to 100,000 cells/particles s^{-1}. Through the use of an optical array of filters and dichroic mirrors, different wavelengths of fluorescent light can be separated and detected simultaneously. In addition, a number of lasers with different excitation wavelengths may be used. Hence, a variety of fluorophores can be used to target and examine, for example, intra- and extra-cellular properties of

individual cells. The scattered light measurements can also classify an individual carrier's size, shape, granularity and/or complexity and, hence, belonging to a particular population of interest (Shapiro, 1995, *supra*).

Suitable flow cytometers which may be used in the methods of the present invention include those which measure five to nine optical parameters (see Table 4) using a single excitation laser, commonly an argon ion air-cooled laser operating at 15 mW on its 488 nm spectral line. More advanced flow cytometers are capable of using multiple excitation lasers such as a HeNe laser (633 nm) or a HeCd laser (325 nm) in addition to the argon ion laser (488 or 514 nm). Optical parameters, corresponding to different optically detectable/quantifiable attributes, for a carrier, may be measured by a flow cytometer to provide a matrix of qualitative and/or quantitative information, providing a code (or addressability in a multi-dimensional space) for the carrier.

TABLE 4

Exemplary optical parameters which may be measured by a flow cytometer.

Parameter	Acronym	Detection angle form incident laser beam	Wavelength (nm)
Forward scattered light	FS	2-5°	488*
Side scattered light	SS	90°	488*
"Green" fluorescence	FL1	90°	510-540†
"Yellow" fluorescence	FL2	90°	560-580†
"Red" fluorescence	FL3	90°	>650#

* using a 488 nm excitation laser

† width of bandpass filter

\# longpass filter

For example, Biggs *et al.* (*Cytometry 36:* 36-45, 1999) have constructed an 11-parameter flow cytometer using three excitation lasers and have demonstrated the use of nine distinguishable fluorophores in addition to forward and side scatter measurements for purposes of immunophenotyping (i.e. classifying) cells. The maximum number of

parameters commercially available currently is 17: forward scatter, side scatter and three excitation lasers each with five fluorescence detectors. Whether all of the parameters can be adequately used depends heavily on the extinction coefficients, quantum yields and amount of spectral overlap between all fluorophores (Malemed *et al., "Flow cytometry and sorting"*, 2nd Ed., New York, Wiley-Liss, 1990). However, it will be understood that the present invention is not restricted to any particular flow cytometer or any particular set of parameters. In this regard, the invention also contemplates use in place of a conventional flow cytometer, a microfabricated flow cytometer as, for example, disclosed by Fu *et al.* (*Nature Biotechnology 17:* 1109-1111, 1999).

A flow cytometer with this capacity to sort is known as a "fluorescence-activated cell sorter" (FACS). Accordingly, the step of sorting in the present method of obtaining a population of detectably unique carriers may be effected by flow cytometric techniques such as by fluorescence activated cell sorting (FACS) although with respect to the present invention, FACS is more accurately "fluorescence activated carrier or solid support sorting" (see, for example, *"Methods in Cell Biology"* Vol. 33, Darzynkiewica, Z. and Crissman, H.A., eds., Academic Press) and Dangl and Herzenberg, *J. Immunol. Methods 52:* 1-14, 1982.

The present invention further relates to modified antibodies. Modified antibodies of particular interest are single chain fragments carrying the variable (V) region of an antibody. This is called an scFv antibody fragment. scFv antibody fragments are derived from Fragment antigen binding (Fab) portions of an antibody and comprise only the V region of a heavy chain linked by a stretch of synthetic peptide to a V region light chain.

In a particularly preferred embodiment, antibodies may also be used to purge target cells, either alone or in conjunction with other immune or cytotoxic molecules.

35-LM expression and variation may also be assessed at the nucleic acid level. For example RT-PCR based methods may be employed to monitor expression of nucleic acid molecules in different cell types and tissues. Nucleic acid sequence variation may be

detected by direct DNA sequencing, either manual sequencing or automated fluorescent sequencing, can detect sequence variation. Another approach is the single-stranded conformation polymorphism assay (SSCP) [Orita *et al., Proc. Nat. Acad. Sci. USA 86:* 2776-2770, 1989]. This method can be optimized to detect most DNA sequence variation. The increased throughput possible with SSCP makes it an attractive, viable alternative to direct sequencing for mutation detection on a research basis. The fragments which have shifted mobility on SSCP gels are then sequenced to determine the exact nature of the DNA sequence variation. Other approaches based on the detection of mismatches between the two complementary DNA strands include clamped denaturing gel electrophoresis (CDGE) [Sheffield *et al., Am. J. Hum. Genet. 49:* 699-706, 1991], heteroduplex analysis (HA) [White *et al., Genomics 12:* 301-306, 1992] and chemical mismatch cleavage (CMC) [Grompe *et al., Proc. Natl. Acad. Sci. USA 86:* 5855-5892, 1989]. Other methods which might detect mutations in regulatory regions or which might comprise large deletions, duplications or insertions include the protein truncation assay or the asymmetric assay. A review of methods of detecting DNA sequence variation can be found in Grompe [*Nature Genetics 5:* 111-117, 1993]. Once a mutation is known, an allele specific detection approach such as allele specific oligonucleotide (ASO) hybridization can be utilized to rapidly screen large numbers of other samples for that same mutation. Such a technique can utilize probes which are labeled with gold nanoparticles to yield a visual color result [Elghanian *et al., Science 277:* 1078-1081, 1997]. Techniques are available to screen RNA products or proteinaceous products.

Preferably, the polypeptides encoded by the present nucleic acid molecules are expressed on the surface of defined populations of hematopoietic cells. Cells of leukocyte lineages are contemplated, including, for example, monocytes, dendritic cells, NK cells, granulocytes, T-lymphocytes, B-lymphocytes, monocyte derived dendritic cells and precursors thereof.

The phrase, "differentially expressed" is a broad reference to expression of mRNA or a polypeptide in a particular cell type, organ or tissue, stage of development, differentiation cell cycle, or, wherein expression is varied as a result of age, infection, immune or other

status or an individual.

The present invention provides methods of screening for agents which interact with the 35-LM nucleic acid molecules or polypeptides of the present invention. Competitive binding assays are preferred. Conveniently, high throughput screening of test peptides is used to identify peptides with suitable affinity and selectivity. Purified 35-LM polypeptide may be immobilized or cells or membranes expressing 35-LM polypeptide may be employed.

Following identification of antibodies or natural or artificial agonists and antagonists including scFv fragments, one or more substances may be manufactured or formulated as a composition suitable for administration to individuals in a method of treatment or prophylaxis.

Such compositions can be formulated according to conventional pharmaceutical compounding techniques. See, for example, *Remington's Pharmaceutical Sciences,* 18th Ed. (1990, Mack Publishing, Company, Easton, PA, U.S.A.). The composition may contain the active agent or pharmaceutically acceptable salts of the active agent. These compositions may comprise, in addition to one of the active substances, a pharmaceutically acceptable excipient, carrier, buffer, stabilizer or other materials well known in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. intravenous, oral, intrathecal, epineural or parenteral. For antibodies, parenteral administration is particularly useful.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and

the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The active agent can be encapsulated to make it stable to passage through the gastrointestinal tract while at the same time allowing for passage across the blood brain barrier. See for example, International Patent Publication No. WO 96/11698.

For parenteral administration, the compound may dissolved in a pharmaceutical carrier and administered as either a solution of a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

The active agent is preferably administered in a therapeutically effective amount. The actual amount administered and the rate and time-course of administration will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage, timing, etc. is within the responsibility of general practitioners or specialists and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of techniques and protocols can be found in *Remington's Pharmaceutical Sciences, supra.*

Instead of administering these agents directly, they may also be produced in the target cell, e.g. in a viral vector or in a cell based delivery system such as described in U.S. Patent No. 5,550,050 and International Patent Publication Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. The vector could be targeted to the target cells. The cell based delivery system is designed to be implanted in a patient's body at the desired target site and contains a coding sequence for the target agent. Alternatively, the agent could be

administered in a precursor form for conversion to the active form by an activating agent produced in, or targeted to, the cells to be treated. See, for example, European Patent Application No. 0 425 731A and International Patent Publication No. WO 90/07936.

The present invention is further described by the following non-limiting Examples.

EXAMPLE 1

Identification of CMRF-35 family members

cDNA probes specific for CMRF-35A and CMRF-35H Ig domains were identified as binding to a large number of independent, non-overlapping PAC clones. Partial and full length cDNA molecules which map to human chromosome 17q22-24 were identified from EST and 5' RACE studies. Alignment of the sequences with CMRF-35A and CMRF-35H indicated similarities over the transmembrane region. cDNA and gDNA sequences were also used to further RT-PCR based expression studies. An alignment of the nucleic acid sequences of the human cDNAs is shown in Figure 1. An alignment of the protein sequences of the human cDNAs is shown in Figure 2.

An RT-PCR assay was established to characterize the expression of the novel members of the 35-LM family in normal hematopoietic lineages and cell lines. Screening of public and commercial databases was used to confirm that the EST used for the RT-PCR represents a single exon. The sequence of the complete cDNAs is used to design RT-PCR primers that cross intron-exon junctions. The primers are used to confirm the expression data. This ensures the identification of any splice variants.

EXAMPLE 3

Expression studies for CMRF-35

Figure 3 summarizes the expression analysis of the h35-LMs on cell lines and freshly purified hematopoietic populations.

RT-PCR was performed to determine the expression of h35-L3 (AW8) on cDNA made from RNA isolated from hematopoietic cell lines (leukemic derived) and cells of different hematopoietic lineages. Analysis of hematopoietic cell line data indicate that 35-L3 is expressed by the derived cell lines HEL, HL60, KG-1, Monomac 6, U937 and K562 and the Hodgkins disease derived cell lines HDLM-2 and KM-H2. 35-L3 was not found in lines of T or B cell origin. The RNA for this molecule is predominantly expressed by cells

of the myeloid lineage as shown in Figure 4. Further analysis of dendritic cell populations indicate that 35-L3 (AW8) is expressed only by the $CD11c^+$ myeloid derived DC and not the $CD11c^-$ lymphoid derived DC. Thus, in addition CD33, CD13, and CD14 this molecule appears to be expressed by cells of the myeloid lineage. The inventors have shown that 35-L3 is expressed by leukemic cells from single AML patients. Blast cells from a patient newly diagnosed with AML was selected by flow sorting. RNA isolated from these cells, when used in RT-PCR show the expression of the CMRF-35-L3 specific PCR products.

EXAMPLE 4

Homologs of hCMRF-35 molecules

To locate mouse homologs of h35-LM (i.e. murine orthologs), a series of searches were conducted in the public and commercial databases around the region 11 E2.

Initially, six computationally predicted genes sharing significant homology with h35-LMs were chosen for further analysis. These genes were termed m35a, m35c, m35d, m35f and m35g. Of these, m35a, m35d and m35f contained complete coding regions. Comparison to mouse ESTs in NCBI provided overlapping sequences from which a complete coding sequence could be obtained for m35c and m35g. The ESTs were as follows: 3' end of m35c (gi: 16445999) and middle region of m35g (EST gi: 15562326).

Further database searches revealed two new homologs termed m35h and DIgR2 (86% similar to DIgR1) with NCBI Accession Nos. XM_126721 and XM_126696. Only m35h contained a complete coding region.

The alignment of the nucleic acid sequences of the mouse cDNAs is shown in Figure 4 and the alignment of the protein sequences of the mouse cDNAs is shown in Figure 5.

EXAMPLE 5

Expression analysis of mouse homologs

To study the expression of m35a, m35c, m35d, m35e, m35f, m35g, m35h and DIgR1 in cell lines and freshly prepared haemopoietic cell populations, primers were designed that were specific for each transcript and cross-checked for sequence similarity against other family members. DIgRI was included for comparison to published data (Luo *et al., Biochem. Biophys. Res. Commun. 287:* 35-41, 2001). Optimization of RT-PCR conditions was necessary before analysis of expression could be performed (Table 5).

TABLE 5

Optimization of RT-PCR conditions*

		m35a	m35c	m35d	m35e	m35f	m35g	m35h	DIgR1
A	Optimal RT-PCR conditions	AT: 60°C	AT: 60°C	AT: 60°C	AT: 60°C; 3' primer: 10 mM	AT: 60°C	AT: 60°C	Touchdown $MgCl_2$: 2.0 mM	AT: 60°C
	RT-PCR fragment size	239	266	159	217	142	111	246	244
B	Ig domain RT-PCR conditions	AT: 65°C	AT: 65°C	AT: 65°C	AT: 64°C; 3' primer: 10 mM	AT: 53°C	na	na	na
	Ig RT-PCR fragment size	444	447	393	405	462	na	na	na

* (A) refers to RT-PCRs used for expression analysis while (B) refers to RT-PCRs used for amplification of Ig domains. Only annealing temperature (AT) for RT-PCRs are indicated, unless the PCR cycle varied from standard conditions.

Optimization involved performing a temperature gradient RT-PCR on each primer set, which altered the annealing temperature between 50°C and 65°C. If multiple products were amplified making interpretation difficult, $MgCl_2$ concentrations were titrated between 1.5 mM and 3.5 mM. Further optimization was necessary for m35e, which involved varying forward and reverse primer concentrations and m35h, which involved designing a

touchdown RT-PCR program. The touchdown program contained an initial denaturation of 94°C for 5 min, follwed by 20 cycles of [94°C for 15 sec; 65°C for 15 sec - 0.5°C/cycles; 72°C for 1 min], then 15 cycles of [94°C for 15 sec; 55°C for 15 sec; 72°C for 1 min] and a final extension of 72°C for 5 min. This cycles prevents early false priming, while facilitating amplification, by lowering the annealing temperature in later stage of the program.

The expression of m35a, m35c, m35d, m35e, m35f, m35g, m35h and DIgRI was examined by RT-PCR and Southern blotting (Figure 9 and Figure 7). Amplified template included cDNA synthesized from selected tissues of BALB/c mice, mouse cell lines, C57BL/6 mouse spleen cell subsets and bone marrow derived DCs. Expression of m35-LMs in tissue was generally widespread with only m35d and m35f showing restricted expression for lymphoid tissue. m35a, m35c and DIgR1 were expressed in all tested tissues and m35e and m35h were negative only in skin. Spleen was the only tissue positive for all family members.

EXAMPLE 6

Characterization of the molecular structure of a novel myeloid restricted molecule, 35-L3

Preliminary studies identified the partial sequence of the 35-L3 molecule from an EST database (AW880126). The gene for the molecule has been localized to human chromosome 17. The inventors have established an RT-PCR that identifies this molecule and shows that it is an expressed product. The PCR product has been cloned and sequenced, confirming its identity as the 35-L3 EST. 5' and 3' RACE protocols were used to further identify the full length molecule. PBMC cDNA library in an expression vector, pCMV-SPORT.6 (Life Technologies) is used to isolate a full length clone. PCR and hybridization screening is used. The full length 35-L3 molecule (cDNA) sequence corresponds to an ORF with sequence similarity to the CMRF-35A and CMRF-35H sequences which, in accordance with the present invention, is identified on chromosome 17.

The isolated cDNA(s) is sequenced by Big Dye chain termination sequencing. The 5' RACE data are used to confirm that a full clone has been isolated. The complete sequence of the cDNA is used to analyze the 35-L3 gene structure. Two sequence BLAST searches are performed using the 35-L3 cDNA sequence and the chromosome 17 sequence. This will provide the sequence of the putative promoter region.

RT-PCR has been used to establish the expression of the 35-L3 EST in normal haemopoietic lineages and cell lines. This RT-PCR was designed from a single EST. Screening of the public databases indicates that this EST represents a single exon. The sequence of the complete cDNA is used to design RT-PCR primers that cross intron-exon junctions. These primers are used to confirm the expression data. This will ensure that any splice variants are identified. Variants identified are characterized at the molecular level to determine the presence of alternative exon usage.

EXAMPLE 7

To express 35-L3 and generate monoclonal antibodies (mAb) to 35-L3 to study its expression in leukocytes and other tissues

Constructs are made to allow expression of recombinant forms of the 35-L3 molecule in mammalian and prokaryotic systems. The cDNA isolated from the pCMV-SPORT library is inserted in an expression vector. This is used to transiently transfect COS cells. Mice are immunized using a tolerance procedure (Dzionek *et al., J Immunol 165(11)*: 6037, 2000) that allows the induction of tolerance to the parental COS cells, whilst immunizing against the transfected cells. Expression of the cDNA is monitored by RT-PCR and Northern blotting to ensure at least RNA is transcribed. DNA immunization was also used in place of the tolerance procedure.

The cDNA sequence is used to design PCR primers to produce a range of fragments that is used to make recombinant proteins. These include the potential extracellular domains of the 35-L3 molecule fused to (1) the human IgG1 Fc portion, (2) a HIS tag or (3) a myc tag.

The fusion products are expressed in mammalian cells or *E. coli* as appropriate. The fusion proteins will be purified by affinity chromatography using protein A for IgG1 Fc fusion proteins, and anti-His or anti myc monoclonal antibodies as appropriate. Purified recombinant proteins are monitored by SDS-PAGE.

The recombinant proteins are used to immunize rabbits to produced rabbit polyclonal serum. Recombinant proteins or cDNA in expression vectors are used to immunize mice to produce mAb. Specific mAb are identified by ELISA using the recombinant fusion proteins or by flow cytometry using RT-PCR expression data to determine appropriate cell lines as targets.

The mAb is used to analyze the expression of the 35-L3 molecule on normal haemopoietic populations by flow cytometry. Basic biochemical characterization (immunoprecipitation or Western Blots) of the 35-L3 molecule is performed to identify its molecular size.

EXAMPLE 8

To analyze 35-L1 to L5 expression in leukemias

Blast populations are isolated from bone marrow or peripheral blood samples of new and relapsed AML and ALL patients. A standard cell surface phenotype of the leukemic cells are determined and this is used in three color analysis to phenotype the cells. If necessary, the leukemic cells are sorted for more detailed phenotypic analysis.

Aliquots of 5 ml peripheral blood is collected from newly diagnosed leukemic patients according to ethical consent. Patients of each subtype is tested and reported according to the new classification.

In addition, sorted blast cells are used to prepare RNA and cDNA for quantitative real time (RT) polymerase chain reaction (PCR) analysis. This allows information to be collected on the expression of the 35-L1, 35-L2, 35-L3, 35-L4 or 35-L5 (referred to as "35-L1 to L5") prior to the generation of monoclonal or polyclonal reagents.

EXAMPLE 9

Functional aspects of 35-L1 to L5 specific mAb

Given the potential of this molecule to be used, for example, as a marker for leukemic cells, mAbs generated herein are assessed for their ability to target or purge 35-L1$^+$ to L5$^+$ cells. Reference to "35-L1 to L5" means any one of 35-L1, 35-L2, 35-L3, 35-L4 or 35-L5 or combinations thereof. The following experiments are performed to assess their potential:

(a) to deliver intracellular toxins or radionuleotides *via* internalization;

(b) to effect the growth of 35-L1$^+$ to L5$^+$ cells in culture; and

(c) their ability to target and lyse 35-L1$^+$ to L5$^+$ and homolog bearing cells.

(a) The ability of the mAb bound to surface 35-L1$^+$ to L5$^+$ to internalize. Biotinylated mAb will be bound to 35-L1$^+$ to L5$^+$ targets. Cells are incubated at 37°C, 4°C with and without fixation. Internalization is assessed by flow cytometry. In addition, these assays will allow determination of the shedding or production of soluble 35-L1$^+$ to L5$^+$ protein from the cell surface.

(b) The effects of crosslinking the 35-L1$^+$ to L5$^+$ mAb on growth kinetics, cell cycle disruption or apoptosis will also be assayed on leukemic cell lines and AML samples. Apoptosis is assessed by Annexin V staining or expression of the bcl-2 molecule by cells in culture.

(c) Complement dependent cytotoxicity of 35-L1$^+$ to L5$^+$ targets using anti-35-L1$^+$ to L5$^+$ mAb and complement is assayed. Targets to be used for this analysis depend on the results of AIM 2.The ability of the mAb to lyse tumor cells *via* antibody dependent cell mediated cytotoxicity (ADCC) is also tested using standard assays. Assays for complement dependent cytotoxicity (CDC) and ADCC have been developed for assessing the ability of the CMRF-44 mAb to lyse target cells.

In a variation of this assay, CMRF-35A or CMRF-35H is crosslinked with 35-LM antibodies.

EXAMPLE 10

In vivo model

A NOD-SCID mouse model is developed to conduct *in vivo* assays on AML. Such a model provides valuable information of the *in vivo* effects of antagonists and agonists of 35-L1 to L5 (e.g. 35-L1 to L5 mAbs).

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

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Ala Leu Ser Lys Cys Arg Thr Val Ala Gly Pro Trp Gly Ser Leu Ser
20 25 30

Val Gln Cys Pro Tyr Glu Lys Glu His Arg Thr Leu Asn Lys Tyr Trp
35 40 45

Cys Arg Pro Pro Gln Ile Phe Leu Cys Asp Lys Ile Val Glu Thr Lys
50 55 60

Gly Ser Ala Gly Lys Arg Asn Gly Arg Val Ser Ile Arg Asp Ser Pro
65 70 75 80

Ala Asn Leu Ser Phe Thr Val Thr Leu Glu Asn Leu Thr Glu Glu Asp
85 90 95

Ala Gly Thr Tyr Trp Cys Gly Val Asp Thr Pro Trp Leu Arg Asp Phe
100 105 110

His Asp Pro Val Val Glu Val Glu Val Ser Val Phe Pro Ala Ser Thr
115 120 125

Ser Met Thr Pro Ala Ser Ile Thr Ala Ala Lys Thr Ser Thr Ile Thr
130 135 140

Thr Ala Phe Pro Pro Val Ser Ser Thr Thr Leu Phe Ala Val Gly Ala
145 150 155 160

Thr His Ser Ala Ser Ile Gln Glu Glu Thr Glu Glu Val Val Asn Ser
165 170 175

Gln Leu Pro Leu Leu Leu Ser Leu Leu Ala Leu Leu Leu Leu Leu Leu
180 185 190

Val Gly Ala Ser Leu Leu Ala Trp Arg Met Phe Gln Lys Trp Ile Lys
195 200 205

Trp Ile Lys Ala Gly Asp His Ser Glu Leu Ser Gln Asn Pro Lys Gln
210 215 220

Ala Ala Thr Gln Ser Glu Leu His Tyr Ala Asn Leu Glu Leu Leu Met
225 230 235 240

Trp Pro Leu Gln Glu Lys Pro Ala Pro Pro Arg Glu Val Glu Val Glu
245 250 255

Tyr Ser Thr Val Ala Ser Pro Arg Glu Glu Leu His Tyr Ala Ser Val
260 265 270

Val Phe Asp Ser Asn Thr Asn Arg Ile Ala Ala Gln Arg Pro Arg Glu
275 280 285

Glu Glu Pro Asp Ser Asp Tyr Ser Val Ile Arg Lys Thr
290 295 300

<210> 5
<211> 674
<212> DNA
<213> homosapiens

<400> 5
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gctctgtgac tggcactgcg ggggactctc tgacagtgtg gtgtcagtat gagagcatgt 180

acaagggata taacaagtac tggtgccgag gacagtacga cacgtcatgt gagagcattg 240

tggagaccaa gggagaagag aaggtggaga ggaatggccg cgtgtccatc agagaccacc 300

cggaggctct cgccttcact gtgaccatgc agaacctcaa tgaagatgat gctggatctt 360

actggtgcaa aattcagaca gtgtgggtcc tggattcatg gtcacgcgat ccctcggacc 420

tggttagggt gtatgtttcc ccagcaatta caaccccaag gaggaccaca catccagcca 480

cacctcccat cttcctggtg gtgaaccctg ggcgaaacct cagcaccagg gaggtgttga 540

cccaaaattc agggttccgg ctcagcagcc ctcacttcct gctcgtggtc cttctgaagc 600

tgcccctgct cctgagcatg ctgggtgctg ttttctgggt gaacaggcct cagtgggctc 660

ctcctggaag atag 674

<210> 6
<211> 205
<212> PRT
<213> homosapiens

<400> 6

Met Trp Leu Leu Pro Ala Leu Leu Leu Leu Cys Leu Ser Gly Cys Leu
1 5 10 15

Ser Leu Lys Gly Pro Gly Ser Val Thr Gly Thr Ala Gly Asp Ser Leu
20 25 30

Thr Val Trp Cys Gln Tyr Glu Ser Met Tyr Lys Gly Tyr Asn Lys Tyr
35 40 45

Trp Cys Arg Gly Gln Tyr Asp Thr Ser Cys Glu Ser Ile Val Glu Thr
50 55 60

Lys Gly Glu Glu Lys Val Glu Arg Asn Gly Arg Val Ser Ile Arg Asp
65 70 75 80

His Pro Glu Ala Leu Ala Phe Thr Val Thr Met Gln Asn Leu Asn Glu
85 90 95

Asp Asp Ala Gly Ser Tyr Trp Cys Lys Ile Gln Thr Val Trp Val Leu
100 105 110

Asp Ser Trp Ser Arg Asp Pro Ser Asp Leu Val Arg Val Tyr Val Ser
115 120 125

Pro Ala Ile Thr Thr Pro Arg Arg Thr Thr His Pro Ala Thr Pro Pro
130 135 140

Ile Phe Leu Val Val Asn Pro Gly Arg Asn Leu Ser Thr Arg Glu Val
145 150 155 160

Leu Thr Gln Asn Ser Gly Phe Arg Leu Ser Ser Pro His Phe Leu Leu
165 170 175

Val Val Leu Leu Lys Leu Pro Leu Leu Leu Ser Met Leu Gly Ala Val
180 185 190

Phe Trp Val Asn Arg Pro Gln Trp Ala Pro Pro Gly Arg
195 200 205

<210> 7
<211> 510
<212> DNA
<213> homosapiens

<400> 7
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atcactggtc caacaacagt gaatggctcg gagcagggct cattgactgt gcagtgtgct 120

tatggctcag gctgggagac ctacttgaag tggcggtgtc aaggagctga ttggaattac 180

tgtaacatcc ttgttaaaac aaatggatca gagcaggagg taaagaagaa tcgagtttcc 240

atcagggaca atcagaaaaa ccacgtgttc accgtgacca tggagaatct caaaagagat 300

gatgctgaca gttattggtg tgggactgag agacctggaa ttgatcttgg ggtcaaagtt 360

caagtgacca ttaacccagc tcagtgcctg agtctgttgc ccacagatga cagggtgatg 420

gttccagttt cagcccacag gccaaaggga ccccccttccc tggtaaccag agaccccaat 480

ccctgccagt gccttcttgg aacttcttta 510

<210> 8
<211> 174
<212> PRT
<213> homosapiens

<400> 8

Met Trp Leu Ser Pro Ala Leu Leu Leu Leu Ile Leu Pro Gly Tyr Ser
1 5 10 15

Ile Ala Ala Lys Ile Thr Gly Pro Thr Thr Val Asn Gly Ser Glu Gln
20 25 30

Gly Ser Glu Gln Gly Ser Leu Thr Val Gln Cys Ala Tyr Gly Ser Gly

35 40 45

Trp Glu Thr Tyr Leu Lys Trp Arg Cys Gln Gly Ala Asp Trp Asn Tyr
50 55 60

Cys Asn Ile Leu Val Lys Thr Asn Gly Ser Glu Gln Glu Val Lys Lys
65 70 75 80

Asn Arg Val Ser Ile Arg Asp Asn Gln Lys Asn His Val Phe Thr Val
85 90 95

Thr Met Glu Asn Leu Lys Arg Asp Asp Ala Asp Ser Tyr Trp Cys Gly
100 105 110

Thr Glu Arg Pro Gly Ile Asp Leu Gly Val Lys Val Gln Val Thr Ile
115 120 125

Asn Pro Ala Gln Cys Leu Ser Leu Leu Pro Thr Asp Asp Arg Val Met
130 135 140

Val Pro Val Ser Ala His Arg Pro Lys Gly Pro Pro Ser Leu Val Thr
145 150 155 160

Arg Asp Pro Asn Pro Cys Gln Cys Leu Leu Gly Thr Ser Leu
165 170

<210> 9
<211> 1026
<212> DNA
<213> homosapiens

<400> 9
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gagaaggaac cgagaagatg tagaaggaaa aagagcctca gacccttgct gcccacaagg 120

acttcccatg ttgtgagatg acccagaggg ctggggctgc catgctgcct tcagctctgc 180

tccttctctg tgtcccaggc tgtctgactg tgagtggccc cagcaccgtg atgggcgccg 240

tgggggaatc cctgagtgtt cagtgtcggt atgaagacaa atacaagacg tttaacaaat 300

actggtgcag acaaccatgc ttgccaattt ggcatgaaat ggtggagacc ggagggtctg 360

agggagtggt gaggagtgac caagtgatca tcacggacca tcctggagac ctcaccttca 420

ccgtgacctt ggagaacctc acggcagacg atgcaggaaa ataccgatgt gggattgcaa 480

caatactgca ggaagatggc ctgtctggtt tcctgcccga tcccttcttc caggttcaag 540

tgctggtctc atcggcctcc agtactgaga actctgtgaa gacacctgca tctcccacca 600

ggcccagcca atgccaaggg tccctgccca gcagcacctg cttcctgctt ctcccactcc 660

tgaaggtgcc tctgctcctg agcatactcg gtgctatcct ctgggtgaac aggccttgga 720

ggactccttg gacagagtca tgaacaggag aacttgcaac accccatgcc cattggaacc 780

ctgtccagag acacagcccc tctgactgca aaaaggactt ctgaccctga ccctcatatt 840

tctttccatc ttatcacccg gatacttttt aaaagttaaa aaaaaaatgt aggccgggtg 900

cggtggctta cacctgcaat cccagcactt tgggaggcca aggcaaggtg gatcacttga 960

gtccagggaa gtttgagagc ctgggcagca tggtcagacc tcatctctac aaaaaaaaaa 1020

aaaaag 1026

<210> 10
<211> 193
<212> PRT
<213> homosapiens

<400> 10

Met Leu Pro Ser Ala Leu Leu Leu Leu Cys Val Pro Gly Cys Leu Thr
1 5 10 15

Val Ser Gly Pro Ser Thr Val Met Gly Ala Val Gly Glu Ser Leu Ser
20 25 30

Val Gln Cys Arg Tyr Glu Asp Lys Tyr Lys Thr Phe Asn Lys Tyr Trp
35 40 45

Cys Arg Gln Pro Cys Leu Pro Ile Trp His Glu Met Val Glu Thr Gly
50 55 60

Gly Ser Glu Gly Val Val Arg Ser Asp Gln Val Ile Ile Thr Asp His
65 70 75 80

Pro Gly Asp Leu Thr Phe Thr Val Thr Leu Glu Asn Leu Thr Ala Asp
85 90 95

Asp Ala Gly Lys Tyr Arg Cys Gly Ile Ala Thr Ile Leu Gln Glu Asp
100 105 110

Gly Leu Ser Gly Phe Leu Pro Asp Pro Phe Phe Gln Val Gln Val Leu

115 120 125

Val Ser Ser Ala Ser Ser Thr Glu Asn Ser Val Lys Thr Pro Ala Ser
130 135 140

Pro Thr Arg Pro Ser Gln Cys Gln Gly Ser Leu Pro Ser Ser Thr Cys
145 150 155 160

Phe Leu Leu Leu Pro Leu Leu Lys Val Pro Leu Leu Leu Ser Ile Leu
165 170 175

Gly Ala Ile Leu Trp Val Asn Arg Pro Trp Arg Thr Pro Trp Thr Glu
180 185 190

Ser

<210> 11
<211> 1352
<212> DNA
<213> homosapiens

<400> 11
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atctgcattt gccactggtt gcagatcagg cggacgagga gccgggaagg cagagccatg 120

tggctgcccc ctgctctgct ccttctcagc ctctcaggct gtttctccat ccaaggccca 180

gagtctgtga gagccccaga gcaggggtcc ctgacggttc aatgccacta taagcaagga 240

tgggagacct acattaagtg gtggtgccga ggggtgcgct gggatacatg caagatcctc 300

attgaaacca gagggtcgga gcaaggagag aagagtgacc gtgtgtccat caaggacaat 360

cagaaagacc gcacgttcac tgtgaccatg gaggggctca ggcgagatga cgcagatgtt 420

tactggtgtg ggattgaaag aagaggacct gaccttggga ctcaagtgaa agtgatcgtt 480

gacccagagg gagcggcttc cacaacagca agctcaccta ccaacagcaa tatggcagtg 540

ttcatcggct cccacaagag gaaccactac atgctcctgg tatttgtgaa ggtgcccatc 600

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aggtcctctc ctgagccacc atcacctcct ggggtgccag cacctgttct cttggtcagg 960

agctgtagag atggagctca agcactggac gactctgtcc ccactgctgg aataactcgg 1020

gcacagagca tgggaccaaa gtacagaaag aggttggggg agacccccc agccctagac 1080

ttccatcatt ccggagacca actcaacacc gtctttgcct gagaacctga tatatccgtg 1140

tttttaaatt ttttttttc tagcaaagtt gggttttaat gacttatgtt cataggaaac 1200

ctctctgatc ccacacacaa ggagggtgat tctgggatga gttcctggtt ctagggcatg 1260

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ggcaatggga acctccctgg cccggcccgg tg 1352

<210> 12
<211> 201
<212> PRT
<213> homosapiens

<400> 12

Met Trp Leu Pro Pro Ala Leu Leu Leu Ser Leu Ser Gly Cys Phe
1 5 10 15

Ser Ile Gln Gly Pro Glu Ser Val Arg Ala Pro Glu Gln Gly Ser Leu
20 25 30

Thr Val Gln Cys His Tyr Lys Gln Gly Trp Glu Thr Tyr Ile Lys Trp
35 40 45

Trp Cys Arg Gly Val Arg Trp Asp Thr Cys Lys Ile Leu Ile Glu Thr
50 55 60

Arg Gly Ser Glu Gln Gly Glu Lys Ser Asp Arg Val Ser Ile Lys Asp
65 70 75 80

Asn Gln Lys Asp Arg Thr Phe Thr Val Thr Met Glu Gly Leu Arg Arg
85 90 95

Asp Asp Ala Asp Val Tyr Trp Cys Gly Ile Glu Arg Arg Gly Pro Asp
100 105 110

Leu Gly Thr Gln Val Lys Val Ile Val Asp Pro Glu Gly Ala Ala Ser
115 120 125

Thr Thr Ala Ser Ser Pro Thr Asn Ser Asn Met Ala Val Phe Ile Gly
130 135 140

Ser His Lys Arg Asn His Tyr Met Leu Leu Val Phe Val Lys Val Pro
145 150 155 160

Ile Leu Leu Ile Leu Val Thr Ala Ile Leu Trp Leu Lys Gly Ser Gln
165 170 175

Arg Val Pro Glu Glu Pro Gly Glu Gln Pro Ile Tyr Met Asn Phe Ser
180 185 190

Glu Pro Leu Thr Lys Asp Met Ala Thr
195 200

<210> 13
<211> 812
<212> DNA
<213> homosapiens

<400> 13
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tgccaggctc cactgagggg aacggggacc tgtctgaaga gaagatgccc ctgctgacac 120

tctacctgct cctcttctgg ctctcaggct actccattgt cactcaaatc accggtccaa 180

caacagtgaa tggcttggag cggggctcct tgaccgtgca gtgtgtttac agatcaggct 240

gggagaccta cttgaagtgg tggtgtcgag gagctatttg gcgtgactgc aagatccttg 300

ttaaaaccag tgggtcagag caggaggtga agagggaccg ggtgtccatc aaggacaatc 360

agaaaaaccg cacgttcact gtgaccatgg aggatctcat gaaaactgat gctgacactt 420

actggtgtgg aattgagaaa actggaaatg accttggggt cacagttcaa gtgaccattg 480

acccagcacc agtcacccaa gaagaaacta gcagctcccc aactctgacc ggccaccact 540

tggacaacag gcacaagctc ctgaagctca gtgtcctcct gcccctcatc ttcaccatat 600

tgctgctgct tttggtggcc gcctcactct tggcttggag gatgatgaag taccagcaga 660

aaggtgagag gacctgggta ctgcagcccc tggagggcga cctctgctat gcagacctga 720

ccctgcagct ggccggaacc tccccgcaaa aggctaccac gaagctttcc tctgcccagg 780

ttgaccaggt ggaagtggaa tatgtcacca tg 812

<210> 14

<211> 287
<212> PRT
<213> homosapiens

<400> 14

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Met Pro Leu Leu Thr Leu Tyr Leu Leu Leu Phe Trp Leu Ser Gly Tyr
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Ser Ile Val Thr Gln Ile Thr Gly Pro Thr Thr Val Asn Gly Leu Glu
            20                  25                  30

Arg Gly Ser Leu Thr Val Gln Cys Val Tyr Arg Ser Gly Trp Glu Thr
        35                  40                  45

Tyr Leu Lys Trp Trp Cys Arg Gly Ala Ile Trp Arg Asp Cys Lys Ile
    50                  55                  60

Leu Val Lys Thr Ser Gly Ser Glu Gln Glu Val Lys Arg Asp Arg Val
65                  70                  75                  80

Ser Ile Lys Asp Asn Gln Lys Asn Arg Thr Phe Thr Val Thr Met Glu
                85                  90                  95

Asp Leu Met Lys Thr Asp Ala Asp Thr Tyr Trp Cys Gly Ile Glu Lys
            100                 105                 110

Thr Gly Asn Asp Leu Gly Val Thr Val Gln Val Thr Ile Asp Pro Ala
        115                 120                 125

Pro Val Thr Gln Glu Glu Thr Ser Ser Ser Pro Thr Leu Thr Gly His
    130                 135                 140

His Leu Asp Asn Arg His Lys Leu Leu Lys Leu Ser Val Leu Leu Pro
145                 150                 155                 160

Leu Ile Phe Thr Ile Leu Leu Leu Leu Leu Val Ala Ala Ser Leu Leu
                165                 170                 175

Ala Trp Arg Met Met Lys Tyr Gln Gln Lys Gly Glu Arg Thr Trp Val
            180                 185                 190

Leu Gln Pro Leu Glu Gly Asp Leu Cys Tyr Ala Asp Leu Thr Leu Gln
        195                 200                 205
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Leu Ala Gly Thr Ser Pro Gln Lys Ala Thr Thr Lys Leu Ser Ser Ala
210 215 220

Gln Val Asp Gln Val Glu Val Glu Tyr Val Thr Met Ala Ser Leu Pro
225 230 235 240

Lys Glu Asp Ile Ser Tyr Ala Ser Leu Thr Leu Gly Ala Glu Asp Gln
245 250 255

Glu Pro Thr Tyr Cys Asn Met Gly His Leu Ser Ser His Leu Pro Gly
260 265 270

Arg Gly Pro Glu Glu Pro Thr Glu Tyr Ser Thr Ile Ser Arg Pro
275 280 285

<210> 15
<211> 2389
<212> DNA
<213> homosapiens

<400> 15
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ccctgaaggg tccaaaggag atcagtggat ttgaaggtga caccgtgtcc ctgcggtgta 180

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tgtcacgctg cggtgacatt gtctacgcaa atcaggacca ggaggtgact cgaggcagga 300

tgtccatccg agacagtccc caagagctct cgatgaccgt gatcatgagg gaccttaccc 360

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aggttacact cattgtcttt ccagggagct cccgtccagt cgtctggctg ccccttacca 480

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agaagaacga gaaggtctac cttgaaacct cgctgccagg gaacggctgg accactgaag 720

actcgacgat agaccttgca gtgactcctg aatgtctcag aaacctcaac ccttctgctg 780

tgccctctcc tgagacacag aacctcagtc agtctacaga ggaggaagag gcagctcgtt 840

ccctggacga cgacaaggag gacgtgatgg caccccctcc cttgcagatg tctgcggagg 900

aactggcctt ctctgagttc atctctgtgt aattgcagaa tgccccgtgg tcggccaggg 960

attgtgaagc tgaacagctg agttctcatg aattcttggg ttctactcac agtccacggc 1020

tctgtccacc ttccttccgg ctctctttca tgccccagat ggagaagtgt cttggtccct 1080

gaagcccgga tggtacttaa caagtccagc cagaggctgg aacctcccgc atattctaat 1140

ccctgggaag agttaatggg tgtgtgggcc ttcatcgggg cctggccagg ctccatggat 1200

aaaggctgag tttgtgtgcg ttccaggaaa ttccctgggc atggatgtcc agcaacagtc 1260

ccacctccca tcctcggaag atcccacctt cacctcctcc agcaacagtc ccacctccca 1320

tcctcggaag atcccacctt cacctccctc taattcttct gcatcaattg ctatggagga 1380

gacaacatat gtgtgtctat gaaacacctg catcctggcc tcttagaaaa taattaaaac 1440

aaaattctgc agacccatca agactcacca aaccatctct agggcagggc ctgggactcc 1500

acagttctga caagtgaccc tgccattcct acccttgggt ctgatgaatc ctcagcccat 1560

tttagctaga atcttccttc cttccttcct tccttccttc cttccttcct tccttccttt 1620

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agaagacact agactctagt tactagagga gaatactaaa tccagtactg ttgagtgagg 2040

gaaagatgga ctggctcaac tatttttttt ccttttttcta ttttgttttg aaaagtaaga 2100

tgttgggaag ggaggtgttc agaatataaa acagaaatgt agggagaata caaaagaagt 2160

gctgtttcta ggatcatata taacctcacc aaaccttgtt gacggctctg cctgagcttg 2220

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cgtgttctac gaactttgta caataaactt tctcagctgt gtagtattt 2389

<210> 16
<211> 287
<212> PRT
<213> homosapiens

<400> 16

Met Arg Pro Leu Val Leu Leu Trp Gly Cys Leu Val Leu Pro Gly Tyr
1 5 10 15

Glu Ala Leu Lys Gly Pro Lys Glu Ile Ser Gly Phe Glu Gly Asp Thr
20 25 30

Val Ser Leu Arg Cys Thr Tyr Val Glu Lys Met Lys Glu His Arg Lys
35 40 45

Tyr Trp Cys Arg Gln Gly Gly Ile Leu Val Ser Arg Cys Gly Asp Ile
50 55 60

Val Tyr Ala Asn Gln Asp Gln Glu Val Thr Arg Gly Arg Met Ser Ile
65 70 75 80

Arg Asp Ser Pro Gln Glu Leu Ser Met Thr Val Ile Met Arg Asp Leu
85 90 95

Thr Leu Lys Asp Ser Gly Lys Tyr Trp Cys Gly Ile Asp Arg Leu Gly
100 105 110

Arg Asp Glu Ser Phe Glu Val Thr Leu Ile Val Phe Pro Gly Ser Ser
115 120 125

Arg Pro Val Val Trp Leu Pro Leu Thr Thr Pro Gln Asp Ser Arg Ala
130 135 140

Val Ala Ser Ser Val Ser Lys Pro Ser Val Ser Ile Pro Met Val Arg
145 150 155 160

Met Met Ala Pro Val Leu Ile Leu Leu Ser Leu Leu Leu Ala Ala Gly
165 170 175

Leu Ile Ala Phe Gly Ser His Met Leu Arg Trp Arg Lys Lys Ala Trp
180 185 190

Leu Ala Thr Glu Thr Gln Lys Asn Glu Lys Val Tyr Leu Glu Thr Ser
195 200 205

Leu Pro Gly Asn Gly Trp Thr Thr Glu Asp Ser Thr Ile Asp Leu Ala
210 215 220

Val Thr Pro Glu Cys Leu Arg Asn Leu Asn Pro Ser Ala Val Pro Ser
225 230 235 240

Pro Glu Thr Gln Asn Leu Ser Gln Ser Thr Glu Glu Glu Glu Ala Ala
245 250 255

Arg Ser Leu Asp Asp Asp Lys Glu Asp Val Met Ala Pro Pro Pro Leu
260 265 270

Gln Met Ser Ala Glu Glu Leu Ala Phe Ser Glu Phe Ile Ser Val
275 280 285

<210> 17
<211> 1111
<212> DNA
<213> homosapiens

<400> 17
gaaatgaccc aactggcctc agctgtgtgg ctgcccacgc tgttgctgct gctgctgctt 60

ttttggcttc caggctgtgt ccctctgcat ggtcccagca ccatgacagg aagtgtgggt 120

caatccctga gtgtgtcgtg tcagtatgag gagaaattta agactaagga caaatactgg 180

tgcagagggt cacttaaggt actgtgcaaa gatattgtca agaccagcag ctcagaagaa 240

gctaggagtg gcagagtgac catcagggac catccagaca acctcacctt tacagtgacc 300

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acattggcat taccccagga agagcttcac tattcatccg tggcattcaa ctcccagagg 840

caggattctc acgccaatgg agattctctt catcaacctc aggaccagaa agcagagtac 900

agtgagatcc agaagcccag aaaaggactc tctgaccttt acctgtgact ccttgtcacc 960

tgatcctctc agtggtgact accaggttcc aaggctccct gctggctgct gccctcaatg 1020

tcatgagcct cagtggcttc actaaagatg agcaggagcc agggctctgt gggcacagtc 1080

tcatcccact ggctctctcc tcttagcctg t 1111

<210> 18
<211> 314
<212> PRT
<213> homosapiens

<400> 18

Met Thr Gln Leu Ala Ser Ala Val Trp Leu Pro Thr Leu Leu Leu Leu
1 5 10 15

Leu Leu Leu Phe Trp Leu Pro Gly Cys Val Pro Leu His Gly Pro Ser
20 25 30

Thr Met Thr Gly Ser Val Gly Gln Ser Leu Ser Val Ser Cys Gln Tyr
35 40 45

Glu Glu Lys Phe Lys Thr Lys Asp Lys Tyr Trp Cys Arg Gly Ser Leu
50 55 60

Lys Val Leu Cys Lys Asp Ile Val Lys Thr Ser Ser Ser Glu Glu Ala
65 70 75 80

Arg Ser Gly Arg Val Thr Ile Arg Asp His Pro Asp Asn Leu Thr Phe
85 90 95

Thr Val Thr Tyr Glu Ser Leu Thr Leu Glu Asp Ala Asp Thr Tyr Met
100 105 110

Cys Ala Val Asp Ile Ser Leu Phe Asp Gly Ser Leu Gly Phe Asp Lys
115 120 125

Tyr Phe Lys Ile Glu Leu Ser Val Val Pro Ser Glu Asp Pro Gly Pro
130 135 140

Thr Leu Glu Thr Pro Val Val Ser Thr Ser Leu Pro Thr Lys Gly Pro
145 150 155 160

Ala Leu Gly Ser Asn Thr Glu Asp Arg Arg Glu His Asp Tyr Ser Gln
165 170 175

Gly Leu Arg Leu Pro Ala Leu Leu Ser Val Leu Ala Leu Leu Leu Phe
180 185 190

Leu Leu Val Gly Thr Ser Leu Leu Ala Trp Arg Met Phe Gln Lys Arg
195 200 205

Leu Val Lys Ala Asp Arg His Pro Glu Leu Ser Gln Asn Leu Arg Gln
210 215 220

Ala Ser Glu Gln Asn Glu Cys Gln Tyr Val Asn Leu Gln Leu His Thr
225 230 235 240

Trp Ser Leu Arg Glu Glu Pro Val Leu Pro Ser Gln Val Glu Val Val
245 250 255

Glu Tyr Ser Thr Leu Ala Leu Pro Gln Glu Glu Leu His Tyr Ser Ser
260 265 270

Val Ala Phe Asn Ser Gln Arg Gln Asp Ser His Ala Asn Gly Asp Ser
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Leu His Gln Pro Gln Asp Gln Lys Ala Glu Tyr Ser Glu Ile Gln Lys
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Pro Arg Lys Gly Leu Ser Asp Leu Tyr Leu
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gtctacttcg gccatatgca gaccttcttc agttcagcag ccacactgac tcctgagagg 420

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gttggggcct ttgtgggtgg gctgatgcaa gttccttcct gttctctggc cgtcgccatc 600

tttaccttcg tgctaacact gactcctcct agttcccagg aagcacacag cacaccgtca 660

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20 25 30

Thr Val Gln Cys Arg Tyr Ser Ser Arg Trp Gln Thr Asn Lys Lys Trp
35 40 45

Trp Cys Arg Gly Ala Ser Trp Ser Thr Cys Arg Val Leu Ile Arg Ser
50 55 60

Thr Gly Ser Glu Lys Glu Thr Lys Ser Gly Arg Leu Ser Ile Arg Asp
65 70 75 80

Asn Gln Lys Asn His Ser Phe Gln Val Thr Met Glu Met Leu Arg Gln
85 90 95

Asn Asp Thr Asp Thr Tyr Trp Cys Gly Ile Glu Lys Phe Gly Thr Asp
100 105 110

Arg Gly Thr Arg Val Lys Val Asn Val Tyr Phe Gly His Met Gln Thr
115 120 125

Phe Phe Ser Ser Ala Ala Thr Leu Thr Pro Glu Arg Ala Ala Glu Met
130 135 140

Trp Val Lys Ile Pro Cys Arg Leu Leu Ile Asn Phe Pro Gly Pro Leu
145 150 155 160

Trp Thr Ala Val Gln Thr Trp Cys Leu Leu Thr Cys Arg Arg Gly Leu
165 170 175

Glu Ala Ser Leu Val Gly Ala Phe Val Gly Gly Leu Met Gln Val Pro
180 185 190

Ser Cys Ser Leu Ala Val Ala Ile Phe Thr Phe Val Leu Thr Leu Thr
195 200 205

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Pro Val Ala Ser Lys Glu Glu Met Asn Arg Leu Phe
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ctctgcttcc aaggttgttt gtctctgacg ggccctggct ctgtgtctgg ctacgtagga 240

ggctctctcc gtgtgcagtg tcaatatagt ccatcatata agggctatat gaaatactgg 300

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gaaaagagga gtggcccagt gtccatcaga gaccatgctg cgaactccac catcacagtg 420

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20 25 30

Arg Val Gln Cys Gln Tyr Ser Pro Ser Tyr Lys Gly Tyr Met Lys Tyr
35 40 45

Trp Cys Arg Gly Pro His Asp Thr Thr Cys Lys Thr Ile Val Glu Thr
50 55 60

Asp Gly Ser Glu Lys Glu Lys Arg Ser Gly Pro Val Ser Ile Arg Asp
65 70 75 80

His Ala Ala Asn Ser Thr Ile Thr Val Ile Met Glu Asp Leu Ser Glu
85 90 95

Asp Asp Ala Gly Ser Tyr Trp Cys Lys Ile Gln Thr Ser Phe Ile Trp
100 105 110

Asp Ser Trp Ser Arg Asp Pro Ser Val Ser Val Arg Val Asn Val Phe
115 120 125

Pro Val Asn Ser Gly Gln Asn Leu Arg Ile Ser Thr Asn Val Met Phe
130 135 140

Ile Phe Gln Leu Trp Ser Leu Leu Ser Ser Ile Gln Phe Gln Val Leu
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Val Phe Leu Lys Leu Pro Leu Phe Leu Ser Met Leu Cys Ala Ile Phe
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Trp Val Asn Arg Leu
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gttctctgct ctactcctat tcttcctccc aggctgctgc acggctcagg attcagtcac 180

aggtccagag gaggtgagcg gtcaggagca gggctccttg acagtgcagt gcagatattc 240

ctcatactgg aagggttaca agaagtactg gtgccgagga gttcctcaga gatcatgtga 300

tattcttgtt gaaaccgata aatcagagca gctggtgaag aagaaccgtg tgtccatcag 360

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ccactgtcac actagctatc tgtcccttat tggcaggaca caccctgctt tctttttttct 1560

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Gln Gly Ser Leu Thr Val Gln Cys Arg Tyr Ser Ser Tyr Trp Lys Gly
35 40 45

Tyr Lys Lys Tyr Trp Cys Arg Gly Val Pro Gln Arg Ser Cys Asp Ile
50 55 60

Leu Val Glu Thr Asp Lys Ser Glu Gln Leu Val Lys Lys Asn Arg Val
65 70 75 80

Ser Ile Arg Asp Asn Gln Arg Asp Phe Ile Phe Thr Val Thr Met Glu
85 90 95

Asp Leu Arg Met Ser Asp Ala Gly Ile Tyr Trp Cys Gly Ile Thr Lys
100 105 110

Gly Gly Pro Asp Pro Met Phe Lys Val Asn Val Asn Ile Asp Gln Ala
115 120 125

Pro Lys Ser Ser Met Met Thr Thr Thr Ala Thr Val Leu Lys Ser Ile
130 135 140

Gln Pro Ser Ala Glu Asn Thr Gly Lys Glu Gln Val Thr Gln Ser Lys
145 150 155 160

Glu Val Thr Gln Ser Arg Pro His Thr Arg Ser Leu Leu Ser Ser Ile
165 170 175

Tyr Phe Leu Leu Met Val Phe Val Glu Leu Pro Leu Leu Leu Ser Met
180 185 190

Leu Ser Ala Val Leu Trp Val Thr Arg Pro Gln Arg Cys Phe Gly Arg
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Gly Glu Asn Asp Leu Val Lys Thr His Ser Pro Val Ala
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ggctgaggat ccagtcacag gtccagagga ggtgagcggt caggagcagg gctccttgac 240

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gaaccgtgtg tccatcaggg acaaccagag agacttcatc ttcacagtga ccatggagga 420

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tccccactta tagccaatgt accttggaag gtaccaggca ggctgcttca gggatgctgt 1260

gtaaatcgta tcaacgatga caataatagc aatcaacctt tatttat 1307

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<211> 296
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<213> homosapiens

<400> 26

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20 25 30

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35 40 45

Asp Tyr Lys Lys Tyr Trp Cys Gln Gly Val Pro Gln Arg Ser Cys Lys
50 55 60

Thr Leu Val Glu Thr Asp Ala Ser Glu Gln Leu Val Lys Lys Asn Arg
65 70 75 80

Val Ser Ile Arg Asp Asn Gln Arg Asp Phe Ile Phe Thr Val Thr Met
85 90 95

Glu Asp Leu Arg Met Ser Asp Ala Gly Ile Tyr Trp Cys Gly Ile Thr
100 105 110

Lys Val Pro Thr Met Pro Pro Ile Thr Ser Thr Thr Thr Ile Phe Thr
115 120 125

Val Thr Thr Thr Val Lys Glu Thr Ser Met Phe Pro Thr Leu Thr Ser
130 135 140

Tyr Tyr Ser Asp Asn Gly His Gly Gly Gly Asp Ser Gly Gly Gly Glu
145 150 155 160

Asp Gly Val Gly Asp Gly Phe Leu Asp Leu Ser Val Leu Leu Pro Val
165 170 175

Ile Ser Ala Val Leu Leu Leu Leu Leu Leu Val Ala Ser Leu Phe Ala
180 185 190

Trp Arg Met Val Arg Arg Gln Lys Lys Asp Leu Ser Leu Lys Gln Pro
195 200 205

Arg Thr Ser Pro Gly Ser Ser Trp Lys Lys Gly Ser Ser Met Ser Ser
210 215 220

Ser Gly Lys Asp His Gln Glu Glu Val Glu Tyr Val Thr Met Ala Pro
225 230 235 240

Phe Pro Arg Glu Glu Val Ser Tyr Ala Ala Leu Thr Leu Ala Gly Leu
245 250 255

Gly Gln Glu Pro Thr Tyr Gly Asn Thr Gly Cys Pro Ile Thr His Val
260 265 270

Pro Arg Thr Gly Leu Glu Glu Glu Thr Thr Glu Tyr Ser Ser Ile Arg
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Arg Pro Leu Pro Ala Ala Met Pro
290 295

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<211> 114
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<213> homosapiens

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Trp Lys Asp Tyr Lys Lys Tyr Trp Cys Arg Gly Ala Tyr Trp Lys Ser
        35                  40                  45

Cys Glu Ile Leu Val Glu Thr Asp Ala Ser Glu Gln Leu Val Lys Glu
    50                  55                  60

Asn Arg Val Ser Ile Arg Asp Asp Gln Thr Asp Phe Ile Phe Thr Val
65                  70                  75                  80

Thr Met Glu Asp Leu Arg Met Ser Asp Ala Asp Ile Tyr Trp Cys Gly
                85                  90                  95

Ile Thr Lys Ala Gly Thr Asp Pro Met Phe Lys Val Asn Val Asn Ile
            100                 105                 110

Asp Pro
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DATED this twenty-ninth day of November 2002.

The Corporation of the Trustees of the Order of the Sisters of Mercy in Queensland

by DAVIES COLLISION CAVE

Patent Attorneys for the Applicant

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35-L2           .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5           .......... .......... .......... .......... .......... [SEQ ID NO:13]
35-L4           .......... .......... .......... .......... .......... [SEQ ID NO:11]
35-L3           .......... .......... .......... .......... .......... [SEQ ID NO:9]
35A             CTCTAAAGGC CACTAGCACC CATCCCAGAG CTGTCAGCAC CGGCCTCAGC [SEQ ID NO:1]
35-L1           .......... .......... .......... .......... .......... [SEQ ID NO:5]
35H             .......... .......... .......... .......... .......... [SEQ ID NO:3]
35-L7(AW8)      .......... .......... .......... .......... .......... [SEQ ID NO:9]

                51                                                 100
35-L2           .......... .......... .......... .......... ..........
35-L5           .......... .......... .......... .......... ..........
35-L4           .......... .......... .......... .......... ..........
35-L3           .......... .......... .......... .......... ..........
35A             CCAGGCGGCT CTCTCCCTGA GCTTCCTGTA GCCCTGACCC TCTCCAGCCT
35-L1           .......... .......... .......... .......... ..........
35H             .......... .......... .......... .......... ..........
35-L7(AW8)      .......... .......... .......... .......... ..........
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Figure 1

```
          101                                                 150
35-L2     .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5     .......... .......... .......... .......... .......... [SEQ ID NO:13]
35-L4     .......... .......... .......... .......... ....GTCTAG [SEQ ID NO:11]
35-L3     ..CCACGCGT CCGCTCCGGT ACTCTCCACC AGCTTTGAGA ACCCAAACCC [SEQ ID NO:9]
35A       CAGACCTGAG ACAGGGCTGG ACAAGGAAGC AGAGAGCAGA AGAAAAGCAG. [SEQ ID NO:1]
35-L1     .......... .......... .......... .......... .......... [SEQ ID NO:5]
35H       .......... .......... .......... .......... .......... [SEQ ID NO:3]
35-L7(AW8) .......... .......... .......... .......... .......... [SEQ ID NO:9]

          151                                                 200
35-L2     .......... .......... .......... .......... ..........
35-L5     ....GAAGTT CAAGGGCGAG AGTGAGTACC AGCAGAAGGC TGGGAGTCTG
35-L4     ATGTGCAGAA GGTGCAAGCC AGAGCTCAGG CAGAACTTCC AGAGTGCATC
35-L3     CAGAAGAGGC CAGAGAAGGA ACCGAGAAGA TGTAGAAGGA AAAAGAGCCT
35A       AAGCGAAGCT CAGATCTGCT GGGAGGAAGA TTACATTTTG TCCCCTCCTG
35-L1     .......... .......... .......... .......... ..........
35H       .......... .......... .......... .......... ..........
35-L7(AW8) .......... .......... .......... .......... ..........

          201                                                 250
35-L2     .......... .......... .......... .......... ..........
35-L5     TAGTTTGTTC CTGCTGCCAG GCTCCACTGA GGGGAACGGG GACCTGTCTG
35-L4     TGGGATCTGC ATTTGCCACT GGTTGCAGAT CAGGCGGACG AGGAGCCGGG
35-L3     CAGACCCTTG CTGCCCACAA GGACTTCCCA TGTTGTGAGA TGACCCAGAG
35A       GGGTCTTGCA CAGTGGCAGG TGACATTCGT GTTACAGGAA TGACTGCCAG
35-L1     .....TTGGA TTCCAGCTGG GACCTAGATT TGCTGAGGAC GGAAGCCAAG
35H       .......... .......... .......... .......... ..........
35-L7(AW8) .......... .......... .......... .......... ......TAGC
```

Figure 1 (continued)

```
                251                                                    300
35-L2           .......... .ATGTGGCTG TCCCCAGCTC TGCTGCTTCT CATCCTCCCA [SEQ ID NO:7]
35-L5           AAGAGAAGAT GCCCCTGCTG ACACTCTACC TGCTCCTCTT CTGGCTCTCA [SEQ ID NO:13]
35-L4           AAGGCAGAGC CATGTGGCTG CCCCCTGCTC TGCTCCTTCT CAGCCTCTCA [SEQ ID NO:11]
35-L3           G.GCTGGGGC TGCCATGCTG CCTTCAGCTC TGCTCCTTCT CTGTGTCCCA [SEQ ID NO:9]
35A             G.GCCTGGGC CTCGTGGCGG TCTTCAGCTC TGCTCCTCCT GCTTGTCCCA [SEQ ID NO:1]
35-L1           GAGACAGGAA CATGTGGCTG CTCCCAGCTC TACTCCTTCT CTGCCTCTCA [SEQ ID NO:5]
35H             .......... ........GG AGGAGCTGGG ACTCTGGCTT GTGTTTTCCA [SEQ ID NO:3]
35-L7(AW8)      TATATATTGT AGAAGATAGT CTGACCATGC TGCCCAGGCT GCTCTCAAAC [SEQ ID NO:9]

                301                                                    350
35-L2           GGTTACTCCA TTGCCGCTAA AATCACTGGT CCAACAACAG TGAATGGCTC
35-L5           GGCTACTCCA TTGTCACTCA AATCACCGGT CCAACAACAG TGAATGGCTT
35-L4           GGCTGTTTC. ........TC CATCCAAGGC CCAGAGTCTG TGAGAGCCCC
35-L3           GGCTGTCTGA CTG..... ..TGAGTGGC CCCAGCACCG TGATGGGCGC
35A             GGCTATTTTC CTC..... ..TGAGCCAC CCCATGACCG TGGCGGGCCC
35-L1           GGCTGTTTGT CTC..... ..TGAAGGGC CCCGGCTCTG TGACTGGCAC
35H             GGATGTTTTG CTC..... ..TGAGCAAA TGCAGGACCG TGGCGGGCCC
35-L7(AW8)      TCCTGGACTC AAGTGATCCA CCTGCCTTGG CCTCCTAAAG TGCTGGGATT

                351                                                    400
35-L2           GGAGCAGGGC TCATTGACTG TGCAGTGTGC TTATGGCTCA GGCTGGGAGA
35-L5           GGAGCGGGGC TCCTTGACCG TGCAGTGTGT TTACAGATCA GGCTGGGAGA
35-L4           AGAGCAGGGG TCCCTGACGG TTCAATGCCA CTATAAGCAA GGATGGGAGA
35-L3           CGTGGGGGAA TCCCTGAGTG TTCAGTGTCG GTATGAAGAC AAATACAAGA
35A             CGTGGGGGGA TCCCTGAGTG TGCAGTGTCG CTATGAGAAG GAACACAGGA
35-L1           TGCGGGGGAC TCTCTGACAG TGTGGTGTCA GTATGAGAGC ATGTACAAGG
35H             CGTGGGGGGA TCCCTGAGTG TGCAGTGTCC CTATGAGAAG GAACACAGGA
35-L7(AW8)      GCAGGGGTAA GCCACCGCAC CCGGCCTACA TTTTTTTTTA ACTTTTAAAA
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Figure 1 (continued)

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                401                                                 450
35-L2           CCTACTTGAA GTGGCGGTGT CAAGGAGCTG ATTGGAATTA CTGTAACATC [SEQ ID NO:7]
35-L5           CCTACTTGAA GTGGTGGTGT CGAGGAGCTA TTTGGCGTGA CTGCAAGATC [SEQ ID NO:13]
35-L4           CCTACATTAA GTGGTGGTGC CGAGGGGTGC GCTGGGATAC ATGCAAGATC [SEQ ID NO:11]
35-L3           CGTTTAACAA ATACTGGTGC AGACAACCAT GCTTGCCAAT TTGGCATGAA [SEQ ID NO:9]
35A             CCCTCAACAA ATTCTGGTGC AGACCACCAC AGATTCTCCG ATGTGACAAG [SEQ ID NO:1]
35-L1           GATATAACAA GTACTGGTGC CGAGGACAGT ACGACACGTC ATGTGAGAGC [SEQ ID NO:5]
35H             CCCTCAACAA ATACTGGTGC AGACCACCAC AGATTTTCCT ATGTGACAAG [SEQ ID NO:3]
35-L7(AW8)      AGTATCCGGT GATAAGATGG AAAGAAATAT GAGGGTCAGG GTCAGAAGTC [SEQ ID NO:9]

                451                                                 500
35-L2           CTTGTTAAAA CAAATGGATC AGAGCAGGAG GTAAAGAAGA ATCGAGTTTC
35-L5           CTTGTTAAAA CCAGTGGGTC AGAGCAGGAG GTGAAGAGGG ACCGGGTGTC
35-L4           CTCATTGAAA CCAGAGGGTC GGAGCAAGGA GAGAAGAGTG ACCGTGTGTC
35-L3           ATGGTGGAGA CCGGAGGGTC TGAGGGAGTG GTGAGGAGTG ACCAAGTGAT
35A             ATTGTGGAGA CCAAAGGGTC AG...CAGGG AAAAGGAATG GCCGAGTGTC
35-L1           ATTGTGGAGA CCAAGGGAGA AGAGAAGGTG GAGAGGAATG GCCGCGTGTC
35H             ATTGTGGAGA CCAAAGGGTC AG...CAGGA AAAAGGAACG GCCGAGTGTC
35-L7(AW8)      CTTTTTGCAG TCAGAGGGGC TGTGTCTCTG GACAGG...G TTCCAATGGG

                501                                                 550
35-L2           CATCAGGGAC AATCAGAAAA ACCACGTGTT CACCGTGACC ATGGAGAATC
35-L5           CATCAAGGAC AATCAGAAAA ACCGCACGTT CACTGTGACC ATGGAGGATC
35-L4           CATCAAGGAC AATCAGAAAG ACCGCACGTT CACTGTGACC ATGGAGGGGC
35-L3           CATCACGGAC CATCCTGGAG ACCTCACCTT CACCGTGACC TTGGAGAACC
35A             CATCAGGGAC AGTCCTGCAA ACCTCAGCTT CACAGTGACC CTGGAGAATC
35-L1           CATCAGAGAC CACCCGGAGG CTCTCGCCTT CACTGTGACC ATGCAGAACC
35H             CATCAGGGAC AGTCCTGCAA ACCTCAGCTT CACAGTGACC CTGGAGAATC
35-L7(AW8)      CAT.GGGGAG TTGCAAGTTC TCCTGTTCAT GACTCTGTCC AAGGAGTCCT
```

Figure 1 (continued)

```
                551                                                 600
35-L2           TCAAAAGAGA TGATGCTGAC AGTTATTGGT GTGGGACTGA GAGACCT...  [SEQ ID NO:7]
35-L5           TCATGAAAAC TGATGCTGAC ACTTACTGGT GTGGAATTGA GAAAACT...  [SEQ ID NO:13]
35-L4           TCAGGCGAGA TGACGCAGAT GTTTACTGGT GTGGGATTGA AAGAAGA...  [SEQ ID NO:11]
35-L3           TCACGGCAGA CGATGCAGGA AAATACCGAT GTGGGATTGC AACAATACTG  [SEQ ID NO:9]
35A             TCACAGAGGA GGACGCAGGC ACCTACTGGT GTGGGGTGGA TACACCGTGG  [SEQ ID NO:1]
35-L1           TCAATGAAGA TGATGCTGGA TCTTACTGGT GCAAAATTCA GACAGTGTGG  [SEQ ID NO:5]
35H             TCACAGAGGA GGATGCAGGC ACCTACTGGT GTGGGGTGGA TACACCGTGG  [SEQ ID NO:3]
35-L7(AW8)      CCAAGGCCTG TTCACCCAGA GGATAGCACC GAGTATGCTC AGGAGCAGAG  [SEQ ID NO:9]

                601                                                 650
35-L2           ...GGAATTG ATCTTGGGGT CAAAGTTCAA GTGACCATTA ACCCAGC.TC
35-L5           ...GGAAATG ACCTTGGGGT CACAGTTCAA GTGACCATTG ACCCAGCACC
35-L4           ...GGACCTG ACCTTGGGAC TCAAGTGAAA GTGATCGTTG ACCCAGAGGG
35-L3           CAGGAAGATG GCCTGTCTGG TTTCCTGCCC GATCCCTTCT TCCAGGTTCA
35A             CTCCGAGACT TTCATGATCC CATTGTCGAG GTTGAGGTGT CCGTGTTCCC
35-L1           GTCCTGGATT CATGGTCACG CGATCCCTCG GACCTGGTTA GGGTGTATGT
35H             CTCCGAGACT TTCATGATCC CGTTGTCGAG GTTGAGGTGT CCGTGTTCCC
35-L7(AW8)      GCACCTTCAG GAGTGGCAGA AG..... ..... .....

                651                                                 700
35-L2           AGTGCCTGAG TCTGTTGCCC ACAGATGAC. .AGGGTGATG GTTCCAGTTT
35-L5           AGTCACCCAA GAAGAAACTA GCAGCTCCCC AACTCTGACC GGCCACCACT
35-L4           AGCGGCTTCC ACAACAGCAA GCTCACCTAC CAACAGCAAT ATGGCAGTGT
35-L3           AGTGCTGGTC TCATCGGCCT CCAGTACTGA GAACTCTGTG AAGACACCTG
35A             GGCCGGGACG ACCACAGCCT CCAGCCCCCA GAGCTCCATG GGCACCTCAG
35-L1           TTCCCCAGCA ATTACAACCC CAAG..... GAGGACCACA CATCCAGCCA
35H             GGCATCAACG TCAATGACAC CTGCAAGTAT CACTGCGGCC AAGACCTCAA
35-L7(AW8)      ..... ..... ..... ..... .....
```

Figure 1 (continued)

```
                701                                                 750
35-L2           CAGCCCACAG GCCAAA.... ..GGGACCCC CTTCCCTGGT AACCAGAGAC [SEQ ID NO:7]
35-L5           TGGACAACAG GCACAAGCTC CTGAAGCTCA GTGTCCTCCT GCCCCTCATC [SEQ ID NO:13]
35-L4           TCATCGGCTC CCACAAGAGG AACCACTACA TGCTCCTGGT ATTTGTGAAG [SEQ ID NO:11]
35-L3           CATCTCCCAC CAGGC..... .......... .......... .......... [SEQ ID NO:9]
35A             GTCCTCCCAC GAAGCTGCCC GTGCACACCT GGCCCAGCGT GACCAGAAAG [SEQ ID NO:1]
35-L1           CACCTCCCAT CTTCCTGGTG GTGAACCCTG GGCGAAACCT CAGCACCAGG [SEQ ID NO:5]
35H             CA.ATCACAA CTGCATTTCC ACCTGTATCA TCCACTACCC TGTTTGCAGT [SEQ ID NO:3]
35-L7(AW8)      .......... .......... .......... .......... .......... [SEQ ID NO:9]

                751                                                 800
35-L2           CCCAATCCCT GCCAGTGCCT TCTTGGAA.. .....CTTCT TTA.......
35-L5           TTCACCATAT TGCTGCTGCT TTTGGTGG.. .....CCGCC TCACTCTTGG
35-L4           GTGCCCATCT TGCTCATCTT GGTCACTG.. .....CCATC CTCTGGTTGA
35-L3           .......... ...CCAGCCA ATGCCAAGG. .........G TCCCTGCCCA
35A             GACAGCCCCG AACCCAGCCC ACACCCTGG. .........C TCCCTGTTCA
35-L1           GA......GG TGTTGACCCA AAATTCAGG. .........G TTCCGGCTCA
35H             GGGTGCCACC CACAGTGCCA GCATCCAGGA GGAAACTGAG GAGGTGGTGA
35-L7(AW8)      .......... .......... .......... .......... ..........

                801                                                 850
35-L2           .......... .......... .......... .......... ..........
35-L5           CTTGGAGGAT GATGAAGTAC CAGCAGAAAG GTGAGAGGAC CTGGGTACTG
35-L4           AGGGGTCTCA GAGGGTCCCT GAGGAGCCAG GGGAACAGCC TATCTACATG
35-L3           GCAGCACCTG CTTCCTGCTT CTCCCACTCC TGAAGGTGCC TCTGCTCCTG
35A             GCAATGTCCG CTTCCTGCTC CTGGTCCTCT TGGAGCTGCC CCTGCTCCTG
35-L1           GCAGCCCTCA CTTCCTGCTC GTGGTCCTTC TGAAGCTGCC CCTGCTCCTG
35H             ACTCACAGCT CCCGCTGCTC CTCTCCCTGC TGGCATTGTT GCTGCTTCTG
35-L7(AW8)      .......... .......... .......... .......... ..........
```

Figure 1 (continued)

```
            851                                                 900
35-L2       .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5       ..CAGCCCCT GGAGGGCGAC CTCTGCTATG CAGACCTGAC CCTGCAGCTG [SEQ ID NO:13]
35-L4       AACTTCTCCG AACCTCTGAC TAAAGACATG GCCACTTAGA GAGATGGATC [SEQ ID NO:11]
35-L3       AGCATACTCG GTGCTATCCT CTGGGTGAAC AGGCCTTGGA .......... [SEQ ID NO:9]
35A         AGCATGCTGG GTGCCGTCCT CTGGGTGAAC AGACCTCAGA .......... [SEQ ID NO:1]
35-L1       AGCATGCTGG GTGCTGTTTT CTGGGTGAAC AGGCCTCAGT .......... [SEQ ID NO:5]
35H         TTGGTGGGGG CCTCCCTGCT AGCCTGGAGG ATGTTTCAGA AATGGATCAA [SEQ ID NO:3]
35-L7(AW8)  .......... .......... .......... .......... .......... [SEQ ID NO:9]

            901                                                 950
35-L2       .......... .......... .......... .......... ..........
35-L5       GCCGGAACCT CCCCGCAAAA GGCTACCACG AAGCTTTCCT CTGCCCAGGT
35-L4       TGCAGAGCCT TCCTGCCCTG GCCACGTTTC CAGAAGAGAC TCGGGCTGTG
35-L3       .....GGACT CCTTGGACAG AGTCATGAAC AGGAGAACTT GCAACACCCC
35A         .....GAAGC TCTAGAAGCA GGCAGAATTG GCCCAAGGGT GAGAACCAGT
35-L1       .....GGGCT CCTCCTGGAA GATAG..... .......... ..........
35H         AGCTGGTGAC CATTCAGAGC TGTCCCAGAA CCCCAAGCAG GCTGCCACGC
35-L7(AW8)  .......... .......... .......... .......... ..........

            951                                                1000
35-L2       .......... .......... .......... .......... ..........
35-L5       TGACCAGGTG GAAGTGGAAT ATGTCACCAT G......... ..........
35-L4       GAAGGAACAT CTACGAGTCC TCGGGATGCA GTGACTGAGA TAGGGGCCCT
35-L3       ATGCCCATTG GAACCCTGTC CAGAGACACA GCCCCTCTGA CTGCAAAAAG
35A         AGCATCTGCT GTCCATCAAG GCCCTGTGCT GCAACAGAGC CCCTCT.GGG
35-L1       .......... .......... .......... .......... ..........
35H         AGAGTGAGCT GCACTACGCA AATCTGGAGC TGCTGATGTG GCCTCTGCAG
35-L7(AW8)  .......... .......... .......... .......... ..........
```

Figure 1 (continued)

```
          1001                                                1050
35-L2     .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5     .......... .......... .......... .......... .......... [SEQ ID NO:13]
35-L4     GGGCCTCCGC CCTGGCCTTG GAGCTGGTGG GCACCTCCCT GTTCTGCACA [SEQ ID NO:9]
35-L3     GACTTCTGAC CCTGACCCTC ATATTTCTTT CCATCTTATC ACCCGGATAC [SEQ ID NO:1]
35A       GACTGGAATG ACCTCCTGAC CATCAAGGCC TGCAACAGAG CCCCTCTGGG [SEQ ID NO:5]
35-L1     .......... .......... .......... .......... .......... [SEQ ID NO:3]
35H       GAAAAGCCAG CACCACCAAG GGAGGTGGAG GTGGAATACA GCACTGTGGC [SEQ ID NO:9]
35-L7(AW8) .......... .......... .......... .......... ..........

          1051                                                1100
35-L2     .......... .......... .......... .......... ..........
35-L5     .......... .......... .......... .......... ..........
35-L4     GCTCAGGGAC TTAGCCAGGT CCTCTCCTGA GCCACCATCA CCTCCTGGGG
35-L3     TTTTTAAAAG TTAAAAAAAA AATGTAGGCC GGGTGCGGTG GCTTACACCT
35A       GGACTGGAAT GACCTCCTGA CCACTCCCTC CCGGGCTGCT CTCTCCAACA
35-L1     .......... .......... .......... .......... ..........
35H       CTCCCCCAGG GAAGAACTTC ACTATGCCTC GGTGGTGTTT GATTCTAACA
35-L7(AW8) .......... .......... .......... .......... ..........

          1101                                                1150
35-L2     .......... .......... .......... .......... ..........
35-L5     .......... .......... .......... .......... ..........
35-L4     TGCCAGCACC TGTTCTCTTG GTCAGGAGCT GTAGAGATGG AGCTCAAGCA
35-L3     GCAATCCCAG CACTTTGGGA GGCCAAGGCA AGGTGGATCA CTTGAGTCCA
35A       TCTCCTGGAA TCCTTTGTGA GCCTCCTTCA GCCTTTTCCC TGTGCCCGAT
35-L1     .......... .......... .......... .......... ..........
35H       CCAACAGGAT AGCTGCTCAG AGGCCTCGGG AGGAGGAACC AGATTCAGAT
35-L7(AW8) .......... .......... .......... .......... ..........
```

Figure 1 (continued)

```
            1151                                                    1200
35-L2       .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5       .......... .......... .......... .......... .......... [SEQ ID NO:13]
35-L4       CTGGACGACT CTGTCCCCAC TGCTGGAATA ACTCGGGCAC AGAGCATGGG [SEQ ID NO:11]
35-L3       GGGAAGTTTG AGAGCCTGGG CAGCATGGTC AGACCTCATC TCTACAAAAA [SEQ ID NO:9]
35A         CCAACATGTG ACACATGAGG ACTTTAGAGC ACAATGGATC .......... [SEQ ID NO:1]
35-L1       .......... .......... .......... .......... .......... [SEQ ID NO:5]
35H         TACAGTGTGA TAAGGAAGAC ATAGGCTTTT GTCCTGCCTC GCCATCGGAG [SEQ ID NO:3]
35-L7(AW8)  .......... .......... .......... .......... .......... [SEQ ID NO:9]

            1201                                                    1250
35-L2       .......... .......... .......... .......... ..........
35-L5       .......... .......... .......... .......... ..........
35-L4       ACCAAAGTAC AGAAAGAGGT TGGGGGAGAC CCCCCCAGCC CTAGACTTCC
35-L3       AAAAAAAAAA G......... .......... .......... ..........
35A         .......... .......... .......... .......... ..........
35-L1       .......... .......... .......... .......... ..........
35H         CTCTCATGGG CCCCAGGAAG TCCAGGGACA GCTCCCTTAT ACCTGGCCCA
35-L7(AW8)  .......... .......... .......... .......... ..........

            1251                                                    1300
35-L2       .......... .......... .......... .......... ..........
35-L5       .......... .......... .......... .......... ..........
35-L4       ATCATTCCGG AGACCAACTC AACACCGTCT TTGCCTGAGA ACCTGATATA
35-L3       .......... .......... .......... .......... ..........
35A         .......... .......... .......... .......... ..........
35-L1       .......... .......... .......... .......... ..........
35H         CGTCCTTCTC AGCCTGCCCT CGACAACAGT GACCAACAGA CAGGCAGCTG
35-L7(AW8)  .......... .......... .......... .......... ..........
```

Figure 1 (continued)

```
          1301                                                1350
35-L2     .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5     .......... .......... .......... .......... .......... [SEQ ID NO:13]
35-L4     TCCGTGTTTT TAAATTTTTT TTTTTCTAGC AAAGTTGGGT TTTAATGACT [SEQ ID NO:11]
35-L3     .......... .......... .......... .......... .......... [SEQ ID NO:9]
35A       .......... .......... .......... .......... .......... [SEQ ID NO:1]
35-L1     .......... .......... .......... .......... .......... [SEQ ID NO:5]
35H       GGTTTCCCAG GCCATCCCTC TGTTGCCATC AGCTTGATTG GCTTCCCCGA [SEQ ID NO:3]
35-L7(AW8) .......... .......... .......... .......... .......... [SEQ ID NO:9]

          1351                                                1400
35-L2     .......... .......... .......... .......... ..........
35-L5     .......... .......... .......... .......... ..........
35-L4     TATGTTCATA GGAAACCTCT CTGATCCCAC ACACAAGGAG GGTGATTCTG
35-L3     .......... .......... .......... .......... ..........
35A       .......... .......... .......... .......... ..........
35-L1     .......... .......... .......... .......... ..........
35H       GGGCCAGCAG GGCTGGGGGC TCCGGAGAGC AGCAGGAAGC ACTCCCAGCC
35-L7(AW8) .......... .......... .......... .......... ..........

          1401                                                1450
35-L2     .......... .......... .......... .......... ..........
35-L5     .......... .......... .......... .......... ..........
35-L4     GGATGAGTTC CTGGTTCTAG GGCATGAGGG GCTGGATGGA CCCTGTCCCC
35-L3     .......... .......... .......... .......... ..........
35A       .......... .......... .......... .......... ..........
35-L1     .......... .......... .......... .......... ..........
35H       ACCAGTGCCT GTCGCCTCTT TCCCCTTTGC CCCTGCTTCA TCCCAGCTCT
35-L7(AW8) .......... .......... .......... .......... ..........
```

Figure 1 (continued)

```
          1451                                                1550
35-L2     .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5     .......... .......... .......... .......... .......... [SEQ ID NO:13]
35-L4     AGGGAGGACA TGGCTCTGAG TCCACAGGGC TGAGGAGGCA ATGGGAACCT [SEQ ID NO:11]
35-L3     .......... .......... .......... .......... .......... [SEQ ID NO:9]
35A       .......... .......... .......... .......... .......... [SEQ ID NO:1]
35-L1     .......... .......... .......... .......... .......... [SEQ ID NO:5]
35H       GTGTGTGGAG GACAAAGCTT CTTCCTGCGT GGCTCCAGGA AAAGATGTGG [SEQ ID NO:3]
35-L7(AW8) .......... .......... .......... .......... .......... [SEQ ID NO:9]

          1501                                                1550
35-L2     .......... .......... .......... .......... ..........
35-L5     .......... .......... .......... .......... ..........
35-L4     CCCTGGCCCG GCCCGGTG.. .......... .......... ..........
35-L3     .......... .......... .......... .......... ..........
35A       .......... .......... .......... .......... ..........
35-L1     .......... .......... .......... .......... ..........
35H       CTCACGTAGG TGGCACCTGC CAATAGCTTT GTCAATCACA GCCCCATAGG
35-L7(AW8) .......... .......... .......... .......... ..........

          1551                                                1600
35-L2     .......... .......... .......... .......... ..........
35-L5     .......... .......... .......... .......... ..........
35-L4     .......... .......... .......... .......... ..........
35-L3     .......... .......... .......... .......... ..........
35A       .......... .......... .......... .......... ..........
35-L1     .......... .......... .......... .......... ..........
35H       AACGTCTGGA ATTGCTTGGG AGTTGGGGAG AACTGTCAAG AAGAGTGAAG
35-L7(AW8) .......... .......... .......... .......... ..........
```

Figure 1 (continued)

```
          1601                                                 1650
35-L2     .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5     .......... .......... .......... .......... .......... [SEQ ID NO:13]
35-L4     .......... .......... .......... .......... .......... [SEQ ID NO:11]
35-L3     .......... .......... .......... .......... .......... [SEQ ID NO:9]
35A       .......... .......... .......... .......... .......... [SEQ ID NO:1]
35-L1     .......... .......... .......... .......... .......... [SEQ ID NO:5]
35H       AGAGTGCCAA AGCGGAGATC TGTTCACCTG GGGGCCATGG AGGGGGGACC [SEQ ID NO:3]
35-L7(AW8) .......... .......... .......... .......... .......... [SEQ ID NO:9]

          1651                                                 1700
35-L2     .......... .......... .......... .......... ..........
35-L5     .......... .......... .......... .......... ..........
35-L4     .......... .......... .......... .......... ..........
35-L3     .......... .......... .......... .......... ..........
35A       .......... .......... .......... .......... ..........
35-L1     .......... .......... .......... .......... ..........
35H       CACTAAAGAT CAAGATCAAA GATTCTCCCC ATCTCACAGA CAAGGAAACT
35-L7(AW8) .......... .......... .......... .......... ..........

          1701                                                 1750
35-L2     .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5     .......... .......... .......... .......... .......... [SEQ ID NO:13]
35-L4     .......... .......... .......... .......... .......... [SEQ ID NO:11]
35-L3     .......... .......... .......... .......... .......... [SEQ ID NO:9]
35A       .......... .......... .......... .......... .......... [SEQ ID NO:1]
35-L1     .......... .......... .......... .......... .......... [SEQ ID NO:5]
35H       GAGGCCAGAG GGAGGAGAGA ATTGCTCATG GCTCCAGAAC TGGTGGCAAG [SEQ ID NO:3]
35-L7(AW8) .......... .......... .......... .......... .......... [SEQ ID NO:9]
```

Figure 1 (continued)

```
          1751                                                    1800
35-L2     .......... .......... .......... .......... .......... [SEQ ID NO:7]
35-L5     .......... .......... .......... .......... .......... [SEQ ID NO:13]
35-L4     .......... .......... .......... .......... .......... [SEQ ID NO:11]
35-L3     .......... .......... .......... .......... .......... [SEQ ID NO:9]
35A       .......... .......... .......... .......... .......... [SEQ ID NO:1]
35-L1     .......... .......... .......... .......... .......... [SEQ ID NO:5]
35H       TTTCTCTGGA CTCTTAGGTT TATTTTTAAT ATGAAATATA AAAACAGTTT [SEQ ID NO:3]
35-L7(AW8) .......... .......... .......... .......... .......... [SEQ ID NO:9]

          1801                                          1841
35-L2     .......... .......... .......... .......... .
35-L5     .......... .......... .......... .......... .
35-L4     .......... .......... .......... .......... .
35-L3     .......... .......... .......... .......... .
35A       .......... .......... .......... .......... .
35-L1     .......... .......... .......... .......... .
35H       CAAATATCTT ATTGAGGGAG AAGTAAAAAC TTATTTAAAC A
35-L7(AW8) .......... .......... .......... .......... .
```

Figure 1 (continued)

```
PileUp of: @/home/mmri00/Georgina/.WAG/pileup-26028.26030

Symbol comparison table: GenRunData:pileuppep.cmp  CompCheck: 1254

                 GapWeight: 3.000
           GapLengthWeight: 0.100

pileup.msf  MSF: 336  Type: P  September  4, 19102 09:05  Check: 3277 ..

Name: 35-L5              Len:   336  Check: 3658  Weight:  1.00
Name: 35-L2              Len:   336  Check: 8520  Weight:  1.00
Name: 35-L4        Len:   336  Check: 6004  Weight:  1.00
Name: CMRF-35A     Len:   336  Check: 8028  Weight:  1.00
Name: CMRF-35H     Len:   336  Check: 6906  Weight:  1.00
Name: 35-L1              Len:   336  Check: 3613  Weight:  1.00
Name: 35-L3        Len:   336  Check: 6548  Weight:  1.00

//

                   1                                                50
35-L5              ......MPLL TLYLLLFWLS GYSIVTQITG PTTVN....G LERGSLTVQC [SEQ ID NO:14]
35-L2              .......MWL SPALLLLILP GYSIAAKITG PTTVNGSEQG SEQGSLTVQC [SEQ ID NO:8]
35-L4              .......MWL PPALLLLSLS GCF...SIQG PESV....RA PEQGSLTVQC [SEQ ID NO:12]
CMRF-35A           MTARAWASWR SSALLLLLVP GYF...PLSH PMTVA....G PVGGSLSVQC [SEQ ID NO:2]
CMRF-35H           .......MWL PWALLLLWVP GCF...ALSK CRTVA....G PW.GSLSVQC [SEQ ID NO:4]
35-L1              .......MWL LPALLLLCLS GCL...SLKG PGSVT....G TAGDSLTVWC [SEQ ID NO:6]
35-L3              ........ML PSALLLLCVP GCL...TVSG PSTVM....G AVGESLSVQC [SEQ ID NO:10]
```

Figure 2

```
                51                                                  100
35-L5           VYRSGWETYL KWWCRGAIWR DCKILVKTSG SEQEVKRDRV SIKDNQKNRT [SEQ ID NO:14]
35-L2           AYGSGWETYL KWRCQGADWN YCNILVKTNG SEQEVKKNRV SIRDNQKNHV [SEQ ID NO:8]
35-L4           HYKQGWETYI KWWCRGVRWD TCKILIETRG SEQGEKSDRV SIKDNQKDRT [SEQ ID NO:12]
CMRF-35A        RYEKEHRTLN KFWCRPPQIL RCDKIVETKG SAG.KRNGRV SIRDSPANLS [SEQ ID NO:2]
CMRF-35H        PYEKEHRTLN KYWCRPPQIF LCDKIVETKG SAG.KRNGRV SIRDSPANLS [SEQ ID NO:4]
35-L1           QYESMYKGYN KYWCRGQYDT SCESIVETKG EEKVERNGRV SIRDHPEALA [SEQ ID NO:6]
35-L3           RYEDKYKTFN KYWCRQPCLP IWHEMVETGG SEGVVRSDQV IITDHPGDLT [SEQ ID NO:10]

                101                                                 150
35-L5           FTVTMEDLMK TDADTYWCGI EKT..... ..GNDLGVTV QVTIDPA...
35-L2           FTVTMENLKR DDADSYWCGT ERP..... ..GIDLGVKV QVTINPAQCL
35-L4           FTVTMEGLRR DDADVYWCGI ERR..... ..GPDLGTQV KVIVDPEGAA
CMRF-35A        FTVTLENLTE EDAGTYWCGV DTPWLRD... ..FHDPIVEV EVSVFPAGTT
CMRF-35H        FTVTLENLTE EDAGTYWCGV DTPWLRD... ..FHDPVVEV EVSVFPASTS
35-L1           FTVTMQNLNE DDAGSYWCKI QTVWVLDSWS ...RDPSDLV RVYVSPAITT
35-L3           FTVTLENLTA DDAGKYRCGI ATILQEDGLS GFLPDPFFQV QVLVSSASST

                151                                                 200
35-L5           ..........  .PVTQE.... .......... .ETSSSPTLT GHHLDNRHKL
35-L2           SLLPTDDRVM VPVSAH.... .......... .RPKGPPSLV TRDPNPCQCL
35-L4           S           TTASSP.... .......... .TNSNMAVFI GSHKRNHYML
CMRF-35A        TASSPQSSMG TSGPPTKLPV ...HTWPSVT RKDSPEPSPH PGSLFSNVRF
CMRF-35H        MTPASITAAK TSTITTAFPP VSSTTLFAVG ATHSASIQEE TEEVVNSQLP
35-L1           .........P RRTTHPATPP IFLVVNPGRN LSTREVLTQN SGFRLSSPHF
35-L3           .........E NSVKTPASP. .......... ..TRPSQCQG S..LPSSTCF
```

Figure 2 (continued)

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                201                                                  250
35-L5           LKLSVLLPLI FTILLLLLVA ASLLAWRMMK YQQKGERTWV LQPLEGDLCY [SEQ ID NO:14]
35-L2           LGTSL..... .......... .......... .......... .......... [SEQ ID NO:8]
35-L4           L      VFV KVPILLILVT AILWLKGSQR VPEEPGEQPI YMNFSEPLTK [SEQ ID NO:12]
CMRF-35A        LLLVLLELPL LL....SMLG AVLWVNRPQR S.....SRSR QNWPKGENQ* [SEQ ID NO:2]
CMRF-35H        LLLSLLALLL LLLVGASLLA WRMFQKWIKW IKAGDHSELS QNPKQAATQS [SEQ ID NO:4]
35-L1           LLVVLLKLPL LL....SMLG AVFWVNRPQW APPGR*.... .......... [SEQ ID NO:6]
35-L3           LLLPLLKVPL LL....SILG AILWVNRPWR TPWTES*... .......... [SEQ ID NO:10]

                251                                                  300
35-L5           ADLTLQLAGT SPQKATTKLS SAQVDQVEVE YVTMASLPKE DISYASLTLG
35-L2           .......... .......... .......... .......... ..........
35-L4           DMAT*..... .......... .......... .......... ..........
CMRF-35A        .......... .......... .......... .......... ..........
CMRF-35H        ELHYANLELL MWPLQEKPAP PREVEVEYST VASPREELHY ASVVFDSNTN
35-L1           .......... .......... .......... .......... ..........
35-L3           .......... .......... .......... .......... ..........

                301                                      336
35-L5           AEDQEPTYCN MGHLSSHLPG RGPEEPTEYS TISRP*
35-L2           .......... .......... .......... ......
35-L4           .......... .......... .......... ......
CMRF-35A-protein .......... .......... .......... ......
CMRF-35H-protein RIAAQRPREE EPDSDYSVIR KT*....... ......
35-L1           .......... .......... .......... ......
35-L3           .......... .......... .......... ......
```

Figure 2 (continued)

Cells	35-L1	35-L2	35-L3	35-L4	35-L5
CD3 T lymphocytes	-	?	-	-	-
CD19 B lymphocytes	-	?	+	+	+
CD15 Granulocytes	-	?	-	-	-
CD16 NK cells	-	?	-	-	-
CD14 Monocytes	+	?	+	+	+
Lin- DC	-	?	+	+	+
CD11c+ Myeloid DC	-	?	ND	ND	-
CD11c- Lymphoid DC	-	?	ND	ND	-
MoDC	-	?	+	+	+
MoDC + LPS	-	?	+	+	+
PBMC	+	?	+	+	+

Figure 3

	35-L1	35-L2	35-L3	35-L4	35-L5
Jurkat	-	?	-	-	-
HSB	-	?	-	+	-
Molt4	-	?	-	-	-
Daudi	-	?	+	+	+/-
Raji	-	?	+	-	?
Mann	-	?	-/+	+	-
Wt49	-	?	+	+	-
KG1	-	?	-	-	+
Hel	-	?	+	+	+
HL60	-	?	+	+	+

Figure 3(continued)

	35-L1	35-L2	35-L3	35-L4	35-L5
NB4	-	?	-	-	-
Thp1	-	?	-	-	-
Monomac6	-	?	=	-	-
U937	+	?	+	+	+
K562	-	?	+	-	-
L428	-	?	=	-	-
HDLM-2	-	?	+	-	-
KM-H2	-	?	+	-	-

Figure 3(continued)

Figure 4

```
PileUp of: @/home/mmri00/Georgina/.WAG/pileup-16229.16245

Symbol comparison table: GenRunData:pileupdna.cmp  CompCheck: 6876

                 GapWeight: 5.000
           GapLengthWeight: 0.300

pileup.msf  MSF: 2554  Type: N  September  6, 19102 14:32  Check: 8705 ..

Name: m35-hRNA          Len:  2554  Check: 4672  Weight:  1.00
Name: m35ge-RNA         Len:  2554  Check: 5363  Weight:  1.00
Name: m35-dRNA          Len:  2554  Check: 3690  Weight:  1.00
Name: m35-fRNA          Len:  2554  Check: 2914  Weight:  1.00
Name: m35-aRNA          Len:  2554  Check: 1598  Weight:  1.00
Name: m35c1RNA          Len:  2554  Check:  468  Weight:  1.00

//

           1                                                  50
 m35-hRNA  ..........  ..........  ..........  ..........  ..GAAGTTAC [SEQ ID NO:23]
m35ge-RNA  ..........  ..........  ...CGGGAAG  TGGCTAAAGG  AGGAAGTGCC [SEQ ID NO:25]
 m35-dRNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:19]
 m35-fRNA  AGGAAGTAGC  TCAGAGTGCA  AAGGAAGCAG  ATAAGAAAAA  AACACATGGA [SEQ ID NO:21]
 m35-aRNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:15]
m35c1RNA   ..........  ..........  ..........  ..........  .......... [SEQ ID NO:17]
```

Figure 5

```
          51                                                  100
m35-hRNA  TGAGAGAAGT GAACAAGAGA GACCTAAAGG CAACTCAAGC TGAGCTGCGA [SEQ ID NO:23]
m35ge-RNA GAGTGAGAGT GAGGGAAACC ACAGGACCAG GAGACGCAGG AGTGGAGCAT [SEQ ID NO:25]
m35-dRNA  .......... .......... .......... .......... .......... [SEQ ID NO:19]
m35-fRNA  GAGAACTTGA ACAAGAAGGT GGTTGCCTGG GCTCTGTTAC ACACATCTGG [SEQ ID NO:21]
m35-aRNA  .......... .......... .......... ...CAGCCCG GCAGAAGCTA [SEQ ID NO:15]
m35c1RNA  .......... .......... .......... .......... .......... [SEQ ID NO:17]

          101                                                 150
m35-hRNA  GTCCTCACAG GGTCCTGACA TCTGTCGTCA ACAAGGACAT GAGAGGAGAC
m35ge-RNA GTAGCCTGTT CTCGCTGGCA GGCTCCACCA AGGTGACCCG GTGTGAGAAG
m35-dRNA  .......... .......... .......... .......... ..........
m35-fRNA  ATTCCAGCAG CGACCTGGAG TTTTCTGGAG ACAGTACCCA GTGAG.GCAG
m35-aRNA  AAGCTCAGAA GAGCTCCCAA TTGCAGGCAA CTGCAGTGTC CAGCACCCAC
m35c1RNA  .......... .......... .GAAATGACC CAACTGGCCT CAGCTGTGTG

          151                                                 200
m35-hRNA  GACCATGTGG CAGTTCTCTG CTCTACTCCT ATTCTTCCTC CCAGGCTGCT
m35ge-RNA ATGCATTTGT CATTGCT.GG TCCCCTTTCT CTTCTGGATC ACAGGCTGCT
m35-dRNA  ....ATGTGG CTGTCCCCAG CTTTGCTTCT TCTCAGTTTT CCAGGCTGCC
m35-fRNA  GAGGATGAGG CTATGTGCAG GTCTGCTCCT TCTCTGCTTC CAAGGTTGTT
m35-aRNA  CATGAGGCCT CTGGTCCTGC TATGGGGCTG CCTGGTGCTC CCAGGTTAT.
m35c1RNA  GCTGCCCACG CTGTTGCTGC TGCTGCTGCT TTTTTGGCTT CCAGGCTGT.
```

Figure 5 (continued)

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          201                                                  250
m35-hRNA  GCACGGCTCA GGATTCAGTC ACAGGTCCAG AGGAGGTGAG CGGTCAGGAG [SEQ ID NO:23]
m35ge-RNA GCACGGCTGA GGATCCAGTC ACAGGTCCAG AGGAGGTGAG CGGTCAGGAG [SEQ ID NO:25]
m35-dRNA  TC........ ....TCCATC CAAGGCCCAG CATTGGTGAG GGGTCCAGAG [SEQ ID NO:19]
m35-fRNA  T......... ...GTCTCTG ACGGGCCCTG GCTCTGTGTC TGGCTACGTA [SEQ ID NO:21]
m35-aRNA  .......... .GAAGCCCTG AAGGGTCCAA AGGAGATCAG TGGATTTGAA [SEQ ID NO:15]
m35c1RNA  .......... .GTCCCTCTG CATGGTCCCA GCACCATGAC AGGAAGTGTG [SEQ ID NO:17]

          251                                                  300
m35-hRNA  CAGGGCTCCT TGACAGTGCA GTGCAGATAT TCCTCATACT GGAAGGGTTA
m35ge-RNA CAGGGCTCCT TGACAGTGCA GTGCCGATAT ACCTCAGGCT GGAAGGATTA
m35-dRNA  CAGGGGTCAG TGACTGTGCA ATGTCGCTAT AGCTCAAGAT GGCAAACCAA
m35-fRNA  GGAGGCTCTC TCCGTGTGCA GTGTCAATAT AGTCCATCAT ATAAGGGCTA
m35-aRNA  GGTGACACCG TGTCCCTGCG GTGTACCTAC GTGGAGAAGA TGAAGGAGCA
m35c1RNA  GGTCAATCCC TGAGTGTGTC GTGTCAGTAT GAGGAGAAAT TTAAGACTAA

          301                                                  350
m35-hRNA  CAAGAAGTAC TGGTGCCG.. .AGGAGTTCC TCAGAGATCA TGTGATATTC
m35ge-RNA CAAGAAGTAC TGGTGCCA.. .AGGAGTTCC TCAGAGATCA TGTAAGACTC
m35-dRNA  CAAGAAGTGG TGGTGCCG.. .GGGAGCAAG CTGGAGCACT TGCAGGGTCC
m35-fRNA  TATGAAATAC TGGTGCCG.. .AGGACCGCA TGACACGACG TGTAAAACTA
m35-aRNA  CAGGAAGTAT TGGTGCCGGC AGGGTGGCAT CCTGGTGTCA CGCTGCGGTG
m35c1RNA  GGACAAATAC TGGTGC.... ..AGAGGGTC ACTTAAGGTA CTGTGCAAAG
```

Figure 5 (continued)

```
                351                                                 400
m35-hRNA    TTGTTGAAAC CGATAAATCA GAGCAGCTGG TGAAGAAGAA CCGTGTGTCC [SEQ ID NO:23]
m35ge-RNA   TTGTTGAAAC CGATGCATCA GAGCAGCTGG TGAAGAAGAA CCGTGTGTCC [SEQ ID NO:25]
m35-dRNA    TCATCCGATC CACTGGGTCA GAGAAAGAAA CGAAGAGCGG CCGGCTGTCC [SEQ ID NO:19]
m35-fRNA    TTGTAGAAAC CGACGGAAGT GAGAAAGAAA AGAGGAGTGG CCCAGTGTCC [SEQ ID NO:21]
m35-aRNA    ACATTGTCTA CGCAAATCAG GACCAGGAGG TGACTCGAGG CAGGATGTCC [SEQ ID NO:15]
m35c1RNA    ATATTGTCAA GACCAGCAGC TCAGAAGAAG CTAGGAGTGG CAGAGTGACC [SEQ ID NO:17]

                401                                                 450
m35-hRNA    ATCAGGGACA ACCAGAGAGA CTTCATCTTC ACAGTGACCA TGGAGGATCT
m35ge-RNA   ATCAGGGACA ACCAGAGAGA CTTCATCTTC ACAGTGACCA TGGAGGATCT
m35-dRNA    ATCAGGGACA ATCAGAAAAA TCACTCATTC CAGGTTACCA TGGAGATGCT
m35-fRNA    ATCAGAGACC ATGCTGCGAA CTCCACCATC ACAGTGATCA TGGAGGACCT
m35-aRNA    ATCCGAGACA GTCCCCAAGA GCTCTCGATG ACCGTGATCA TGAGGGACCT
m35c1RNA    ATCAGGGACC ATCCAGACAA CCTCACCTTT ACAGTGACCT ATGAGAGCCT

                451                                                 500
m35-hRNA    GAGGATGAGC GATGCTGGCA TTTACTGGTG TGGAATTACG AAAGGTGGAC
m35ge-RNA   GAGGATGAGC GATGCTGGCA TTTACTGGTG TGGAATTACG AAAGTGCCAA
m35-dRNA    CAGGCAAAAT GACACGGACA CTTACTGGTG TGGTATTGAA AAGTTCGGAA
m35-fRNA    TAGCGAAGAC GATGCTGGGT CTTACTGGTG CAAGATTCAG A.........
m35-aRNA    TACCCTGAAG GATTCAGGGA AGTACTGGTG TGGGATTGAC AGACTGGGCC
m35c1RNA    CACCCTGGAG GATGCAGACA CCTACATGTG TGCGGTGGAT ATATCACTTT
```

Figure 5 (continued)

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                501                                                    550
m35-hRNA        CTGATCCCAT GTTTAAAGTT AATGTGAACA TTGACCAAGC CCCAAAAAGT [SEQ ID NO:23]
m35ge-RNA       CCATGCCCCC CATCACCTCC ACCACCACCA TCTTCACAGT GACAACCACA [SEQ ID NO:25]
m35-dRNA        CTGACCGTGG GACCAGAGTT AAAGTGAACG TCTACTTCGG CCATATGCAG [SEQ ID NO:19]
m35-fRNA        .......... .......... .......... .......CTT CCTTTATCTG [SEQ ID NO:21]
m35-aRNA        GCGATGAGTC TTTTGAGGTT ACACTCATTG TCTTTCCAGG GAGCTCCCGT [SEQ ID NO:15]
m35c1RNA        TTGATGGCTC .CTTGGGGTT CGATAAGTAC TTCAAGATTG AGTTGTCTGT [SEQ ID NO:17]

                551                                                    600
m35-hRNA        TCAATGATG. ......ACCA CCACAGCCAC A.GTTCTGAA ATCCATACAA
m35ge-RNA       GTAAAAGAG. ......ACCA ........GC A.TGTTTCCA ACGCTGACTA
m35-dRNA        ACCTTCTTC. ......AGTT CAGCAGCCAC ACTGACTCCT GAGAGGGCAG
m35-fRNA        GGATTCGTG. ......GTCA CGTGATCCAT CGGTCAGCGT AAGGGTGAAT
m35-aRNA        CCAGTCGTCT GGCTGCCCCT TACCACACCA CAGGACTCCA GGGCTGTAGC
m35c1RNA        GGTTCCAAGT GAGGACCCAG GACCAACACT AGAGACACCT GTGGTGTCCA

                601                                                    650
m35-hRNA        CCAAGCGCTG AGAACACTGG CAAGGAACAA GTGACTCAGA GCAAAGAAGT
m35ge-RNA       GCTACTACTC TGATAACGGG CATGGCGGTG GTGACAGTGG CGGTGGTGAA
m35-dRNA        CAGAGATGTG GGTAAAGATA CCATGTCGAC TTCTAATCAA CTTCCCTGGC
m35-fRNA        GTTTTTCCAG TGAATTCTGG GCAGAACCTG AGGATTAGTA CTAATGTGAT
m35-aRNA        CAGCAGTGTC TCCAAGCCCA GTGTGTCCAT CCCGATGGTC CGCATGATGG
m35c1RNA        C....CAGTC TGCCTACCAA GGGTCCCGCC CTAGGATCCA ACACAGAGGA
```

Figure 5 (continued)

```
                                                                  700
          651
m35-hRNA  GACTCAGAGC AGGCCCCACA CCAGGTCCCT GCTGAGCAGC ATCTACTTCC [SEQ ID NO:23]
m35ge-RNA GATGGCGTCG GTGATGGGTT TCTGGATCTC AGTGTGCTCC TCCCAGTCAT [SEQ ID NO:25]
m35-dRNA  CCACTGTGGA CGGCAGTACA GACATGGTGT CTTCTGACTT GCAGAAGAGG [SEQ ID NO:19]
m35-fRNA  ......GTTC ATCTTCCAAC TGTGGTCCCT GCTCAGCAGC ATCCAGTTCC [SEQ ID NO:21]
m35-aRNA  CCCCAGTCCT GAT.ACTCTT GTCCCTGCTG TTGGCTGCAG GACTAATTGC [SEQ ID NO:15]
m35c1RNA  CCGCCGTGAG CATGACTATT CCCAGGGCTT GAGGCTCCCA GCGCTGTTGT [SEQ ID NO:17]

                                                             750
          701
m35-hRNA  TGCTGATGGT CTTTGTGGAG TTACCCCTGC TCCTGA.... ..GCATGCTC
m35ge-RNA CTCTGCAG.. ..TCCTGTTG CTTCTCCTGT TGGTGG.... ..CCTCGCTC
m35-dRNA  ACTTGAAGCC AGTCTAGTTG GGGCCTTTGT GGGTGGGCTG ATGCAAGTTC
m35-fRNA  AGGTCCTGGT CTTCCTGAAG CTGCCTCTGT TTCTGA.... ..GCATGCTC
m35-aRNA  CTTTGGCAG. ...CCACATG CTCCGGTGGA GAAAGAAAGC TTGGCTGGCC
m35c1RNA  CTGTGTTAGC TCTCCTGCTG TTTCTGTTGG TGGGGACCTC TCTGCTGGCC

                                                             800
          751
m35-hRNA  AGTGCTGTCC TCTGGGTGAC CAGGCCTCAG AGATGCTTTG GGAGAGGTGA
m35ge-RNA TTTGCTTGGA GGATGGTGAG GAGACAGAAG A......... .AAGACCTGT
m35-dRNA  CTTCCTGTTC TCTGGCCGTC GCCATCTTTA CCTTCGTGCT AACACTGACT
m35-fRNA  TGTGCTATCT TCTGGGTGAA CAGACTTTAG GGGGTTCCTG GGGGCAATGT
m35-aRNA  ACAGAGACAC AGAAGAACGA GAAGGTCTAC CTTGAAACCT CGCTGCCAGG
m35c1RNA  TGGAGGATGT TCCAGAAGCG GCTGGTCAA. .......... AGCTGATAGG
```

Figure 5 (continued)

```
          801                                                  850
m35-hRNA  AAATGACCTG GTGAAGACCC ATAGTCCTGT TGCCTAGGAT AGAGAGAAAC [SEQ ID NO:23]
m35ge-RNA CCCTGAAGCA GCCCAGAACC TCCCCTGGCT CCTCTTGGAA AAAGGGCTCC [SEQ ID NO:25]
m35-dRNA  CCTCCTAGTT CCCAGGAAGC ACACAGCACA CCGTCATCAC ACTCAGCCCC [SEQ ID NO:19]
m35-fRNA  AGAGTGACCC ATCCAAGAAC TATGAAGTGA AGCATCCCA. GGAATGCCCT [SEQ ID NO:21]
m35-aRNA  GAACGGCTGG ACCACTGAAG ACTCGACGAT AGACCTTGCA GTGACTCCTG [SEQ ID NO:15]
m35c1RNA  CATCCAGAGC TGTCCCAGAA CCTCAGACAG GCTTCTGAGC AGAATGAGTG [SEQ ID NO:17]

          851                                                  900
m35-hRNA  AGTTCCCAAG AAATGGAAAA TAATCTCTGT CTCTCTGTTG TCTCTGTCTC
m35ge-RNA TCCATGTCCT CCTCTGGCAA GGACCACCAA GAGGAAGTGG AATATGTCAC
m35-dRNA  AGTGGCTTCC AAGGAAGAGA TGAACCGTCT CTTCTAA... ..........
m35-fRNA  GGGAGGAACT CAGTCCTGCA TGCAGACTGG ACTTCATTGT TCTGTGTCTC
m35-aRNA  AATGTCTCAG AAACCTCAAC CCTTCTGCTG TGCCCTCTCC TGAGACACAG
m35c1RNA  CCAGTATGTG AATTTGCAGC TGCACACGTG GTCTCTGAGG GAAGAGCCGG

          901                                                  950
m35-hRNA  ..TGTCTCTG GGGTGTATGT ATGTGTGTGC ATGCACCTTG CCGGGGCAGA
m35ge-RNA CATGGCTCCC TTTCCCAGGG AGGAGGTTTC ATATGCCGCT CTGACTTTGG
m35-dRNA  .......... .......... .......... .......... ..........
m35-fRNA  A......... .......... .......... .......... ..........
m35-aRNA  AAC..CTCAG TCAGTCTACA GAGGAGGAAG AGGCAGCTCG TTCCCTGGAC
m35c1RNA  TGCTACCAAG TCAGGTAGAA GTGGTGGAAT ATAGCACATT GGCATTACCC
```

Figure 5 (continued)

```
                951                                                  1000
m35-hRNA        TGTGTATGTG GGAGACATCT ACTGGAATCA TTCCCTTAGT ATCTGAGACA [SEQ ID NO:23]
m35ge-RNA       CCGGCTTGGG TCAGGAGCCT ACTTATGGCA ATACTGGCTG CCCCATCACC [SEQ ID NO:25]
m35-dRNA        .......... .......... .......... .......... .......... [SEQ ID NO:19]
m35-fRNA        .......... .......... .......... .......... .......... [SEQ ID NO:21]
m35-aRNA        GACGACAAGG AGGACGTGAT GGCACCCCCT CCCTTGCAGA TGTCTGCGGA [SEQ ID NO:15]
m35c1RNA        CAGGAAGAGC TTCAC....T ATTCATCCGT GGCATTCAAC TCCCAGAGGC [SEQ ID NO:17]

                1001                                                 1050
m35-hRNA        GGGTTTCTAA TTGACCAGCA CCTTTGTGTG GTAGGTCAGA CAGCTGGCCA
m35ge-RNA       CATGTTC... .CCAGGACAG GCCTTGAAGA GGAGACCACA GAGTACAGCA
m35-dRNA        .......... .......... .......... .......... ..........
m35-fRNA        .......... .......... .......... .......... ..........
m35-aRNA        GGAACTGGCC TTCTCTGAGT TCATCTCTGT GTAATTGCAG AATGCCCCGT
m35c1RNA        AGGATTCTCA CGCCAATGGA GATTCTCTTC ATCAACCTCA GGACCAGAAA

                1051                                                 1100
m35-hRNA        GGGAACTCCA GGGATCTCCC TGCCTCTACC ATCCATCCTG AGATTGCAAG
m35ge-RNA       GCATCAGGAG GCCCTTGCCT GCAGCCATGC CTTAATCTTG GTCTCTGAAG
m35-dRNA        .......... .......... .......... .......... ..........
m35-fRNA        .......... .......... .......... .......... ..........
m35-aRNA        GGTCGGCCAG GGATTGTGAA GCTGAACAGC TGAGTTCTCA TGAATTCTTG
m35c1RNA        GCAGAGTACA GTGAGATCCA GAAGCCCAGA AAAGGACTCT CTGACCTTTA
```

Figure 5 (continued)

```
          1101                                                 1150
m35-hRNA  CATACACGAG TGCCCTAGCT TAAAAACAAA CAAACAAACA AACACCTTAG [SEQ ID NO:23]
m35ge-RNA GCGGCTTGGA GCATGGATCT TTACATCTGC CTCTGTACCT GCTTCCTTAC [SEQ ID NO:25]
m35-dRNA  .......... .......... .......... .......... .......... [SEQ ID NO:19]
m35-fRNA  .......... .......... .......... .......... .......... [SEQ ID NO:21]
m35-aRNA  GGTTCTACTC ACAGTCCACG GCTCTGTCCA CCTTCCTTCC GGCTCTCTTT [SEQ ID NO:15]
m35c1RNA  CCTGTGACTC CTTGTCACCT GATCCTCTCA GTGGTGACTA CCAGGTTCCA [SEQ ID NO:17]

          1151                                                 1200
m35-hRNA  GTTG...... TAGGGATTGA ACTCATGTCC TTGTACCTGC AAGGAAGGTA
m35ge-RNA CCGGCCCAGC TGGTGACTGG AACTCTGTCC ATCCGTCTCT CATGGCCATC
m35-dRNA  .......... .......... .......... .......... ..........
m35-fRNA  .......... .......... .......... .......... ..........
m35-aRNA  CATGCCCCAG ATGGAGAAGT GTCTTGGTCC CTGAAGCCCG GATGGTACTT
m35c1RNA  AGGCTCCCTG CTGGCTGCTG CCCTCAATGT CATGAGCCTC AGTGGCTTCA

          1201                                                 1250
m35-hRNA  GGCGATTTAC CTGCTGAGCC ATCTCCCCAA TCTGGAGAAG ACTCAATCTA
m35ge-RNA AGCTCTACCT TGCTTGAGCT TGGAGTTCAA CCTCAGGGGG TTCCAGGGAA
m35-dRNA  .......... .......... .......... .......... ..........
m35-fRNA  .......... .......... .......... .......... ..........
m35-aRNA  AACAAGTCCA GCCAGAGGCT GGAACCT.CC CGCATATTCT AATCCCTGGG
m35c1RNA  CTAAAGATGA GCAGGAGCCA GGGCTCTGTG GGCACAGTCT CATCCCACTG
```

Figure 5 (continued)

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```
            1251                                                    1300
m35-hRNA    GTAAAGAACA ACTCATCAGC AGTACCATGG CTCTGATGTG CTGCACAACC [SEQ ID NO:23]
m35ge-RNA   TTAAGGCTCC TTCCACATCC CCACTTATAG CCAATGTACC TTGGAAGGTA [SEQ ID NO:25]
m35-dRNA    .......... .......... .......... .......... .......... [SEQ ID NO:19]
m35-fRNA    .......... .......... .......... .......... .......... [SEQ ID NO:21]
m35-aRNA    AAGAGTTAAT GGGTGTGTGG GCCTTCATCG GGGCCTGGCC AGGCTCCATG [SEQ ID NO:15]
m35c1RNA    GCTCTCTCCT CTTAGCCTGT .......... .......... .......... [SEQ ID NO:17]

            1301                                                    1350
m35-hRNA    AGACTCAGAC TAATCCCACT CCTATAGCAG GGACAGCTGA GTTCTGGAAC
m35ge-RNA   CCAGGCAGGC TGCTTCAGGG ATGCTGTGTA AATCGTATCA ACGATGACAA
m35-dRNA    .......... .......... .......... .......... ..........
m35-fRNA    .......... .......... .......... .......... ..........
m35-aRNA    GATAAAGGCT GAGTTTGTGT GCGTTCCAGG AAATTCCCTG GGCATGGATG
m35c1RNA    .......... .......... .......... .......... ..........

            1351                                                    1400
m35-hRNA    CCATTCATGT GCCCCTCTCT CAGGACATCC TGCAATACCT ATCTGGGGCT
m35ge-RNA   TAATAGCAAT CAACCTTTAT TTAT...... .......... ..........
m35-dRNA    .......... .......... .......... .......... ..........
m35-fRNA    .......... .......... .......... .......... ..........
m35-aRNA    TCCAGCAACA GTCCCACCTC CCATCCTCGG AAGATCCCAC CTTCACCTCC
m35c1RNA    .......... .......... .......... .......... ..........
```

Figure 5 (continued)

```
          1401                                                      1450
m35-hRNA  ATCTTCCACT GATGACTTCC AAAGAAGAAA ATACAAGAAA ACATCACATT [SEQ ID NO:23]
m35ge-RNA ..........  ..........  ..........  ..........  .......... [SEQ ID NO:25]
m35-dRNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:19]
m35-fRNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:21]
m35-aRNA  CTCTAATTCT TCTGCATCAA TTGCTATGGA GGAGACAACA TATGTGTGTC [SEQ ID NO:15]
m35c1RNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:17]

          1451                                                      1500
m35-hRNA  TCTTCTTAGT GTACTAGTTC CTTAGAGGAC ACATGCCAAT ATAAGACTGC
m35ge-RNA ..........  ..........  ..........  ..........  ..........
m35-dRNA  ..........  ..........  ..........  ..........  ..........
m35-fRNA  ..........  ..........  ..........  ..........  ..........
m35-aRNA  TATGAAACAC CTGCATCCTG GCCTCTTAGA AAATAATTAA AACAAAATTC
m35c1RNA  ..........  ..........  ..........  ..........  ..........

          1501                                                      1550
m35-hRNA  GGGCCACCAG CCAGTTGATT GACCAAATAT CTCGGTGATG TGGCCTCACC
m35ge-RNA ..........  ..........  ..........  ..........  ..........
m35-dRNA  ..........  ..........  ..........  ..........  ..........
m35-fRNA  ..........  ..........  ..........  ..........  ..........
m35-aRNA  TGCAGACCCA TCAAGACTCA CCAAACCATC TCTAGGGCAG GGCCTGGGAC
m35c1RNA  ..........  ..........  ..........  ..........  ..........
```

Figure 5 (continued)

```
                1551                                                1600
m35-hRNA        AAGTAGCATA AAGTTTGCCA CTGTCACACT AGCTATCTGT CCCTTATTGG [SEQ ID NO:23]
m35ge-RNA       .......... .......... .......... .......... .......... [SEQ ID NO:25]
m35-dRNA        .......... .......... .......... .......... .......... [SEQ ID NO:19]
m35-fRNA        .......... .......... .......... .......... .......... [SEQ ID NO:21]
m35-aRNA        TCCACAGTTC TGACAAGTGA CCCTGCCATT CCTACCCTTG GGTCTGATGA [SEQ ID NO:15]
m35c1RNA        .......... .......... .......... .......... .......... [SEQ ID NO:17]

                1601                                                1650
m35-hRNA        CAGGACACAC CCTGCTTTCT TTTTTCTCAA CACAGCCCAG TGACTAAGCC
m35ge-RNA       .......... .......... .......... .......... ..........
m35-dRNA        .......... .......... .......... .......... ..........
m35-fRNA        .......... .......... .......... .......... ..........
m35-aRNA        ATCCTCAGCC CATTTTAGCT AGAATCTTCC TTCCTTCCTT CCTTCCTTCC
m35c1RNA        .......... .......... .......... .......... ..........

                1651                                                1700
m35-hRNA        CATTGCAAAC CCAGATGGAG TAGTTGACCT AAGCTTTGTA CCACCTGCTC
m35ge-RNA       .......... .......... .......... .......... ..........
m35-dRNA        .......... .......... .......... .......... ..........
m35-fRNA        .......... .......... .......... .......... ..........
m35-aRNA        TTCCTTCCTT CCTTCCTTCC TTTCCTTCCT TTCCTTCCTT TCCTTCCTTT
m35c1RNA        .......... .......... .......... .......... ..........
```

Figure 5 (continued)

```
                1701                                                1750
m35-hRNA        AGGTCTTCAA GTAGTAGTTA AGCCTTGGTC CCTGAAATCT AGATTGCTCA [SEQ ID NO:23]
m35ge-RNA       .......... .......... .......... .......... .......... [SEQ ID NO:25]
m35-dRNA        .......... .......... .......... .......... .......... [SEQ ID NO:19]
m35-fRNA        .......... .......... .......... .......... .......... [SEQ ID NO:21]
m35-aRNA        CCTTCCTTTC CTTCCTTTCT TCGTTCCTTC CTGCCTTCCC TGTGGGGTTT [SEQ ID NO:15]
m35c1RNA        .......... .......... .......... .......... .......... [SEQ ID NO:17]

                1751                                                1800
m35-hRNA        GTGAGACCAA ATGGGGAGGT CAACTGCAGG AATCAGCTGA TCTCACAGGA
m35ge-RNA       .......... .......... .......... .......... ..........
m35-dRNA        .......... .......... .......... .......... ..........
m35-fRNA        .......... .......... .......... .......... ..........
m35-aRNA        CCTATATGCT TCCTAGACCT AGATCATGAC AGTACGGTCC CAGTAGGCAC
m35c1RNA        .......... .......... .......... .......... ..........

                1801                                                1850
m35-hRNA        GTCACGAACC CACATCACCC CCAAACCCTT CCAGGAATGG TCTCTTCACC
m35ge-RNA       .......... .......... .......... .......... ..........
m35-dRNA        .......... .......... .......... .......... ..........
m35-fRNA        .......... .......... .......... .......... ..........
m35-aRNA        TTCCTGATGC CTCTCTGGTC AGGCACACTA TGGTGACAGC CAGCCCAAGG
m35c1RNA        .......... .......... .......... .......... ..........
```

Figure 5 (continued)

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```
          1851                                                      1900
m35-hRNA  AGGCCCTTCC ACTCTCTCCC TTTTACTCAG ACAAATCTAT TGAATGTCTA [SEQ ID NO:23]
m35ge-RNA ..........  ..........  ..........  ..........  .......... [SEQ ID NO:25]
m35-dRNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:19]
m35-fRNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:21]
m35-aRNA  CAGCCAGGGA TCAGCTGTCT CTCCATCCTC CTTCCCCAAG GCCCTGTGTC [SEQ ID NO:15]
m35c1RNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:17]

          1901                                                      1950
m35-hRNA  AGTAGTTATC ACTCTCCACA TACATGCTCC AAAATAAGAC AGACCCAATT
m35ge-RNA ..........  ..........  ..........  ..........  ..........
m35-dRNA  ..........  ..........  ..........  ..........  ..........
m35-fRNA  ..........  ..........  ..........  ..........  ..........
m35-aRNA  CCTTGCTTTG GTAGGACACT GGAGGAAGTC TCGATATCAT TCCTGTCCAG
m35c1RNA  ..........  ..........  ..........  ..........  ..........

          1951                                                      2000
m35-hRNA  AAAGTCCATA GAGAAGGCCA ATGGGATCAA AGGTAAATAC TCAGGGGAAA
m35ge-RNA ..........  ..........  ..........  ..........  ..........
m35-dRNA  ..........  ..........  ..........  ..........  ..........
m35-fRNA  ..........  ..........  ..........  ..........  ..........
m35-aRNA  AGTGGTTACT CCTCCATGGG GTCTGGAGGC TGAGGGAGAG GAGGAGGAGG
m35c1RNA  ..........  ..........  ..........  ..........  ..........
```

Figure 5 (continued)

```
                2001                                                 2050
m35-hRNA        TGAGTAGTCT CAGCCCACCA GTCTCAGACA TCCTGAGTTC TGCACCATGA [SEQ ID NO:23]
m35ge-RNA       .......... .......... .......... .......... .......... [SEQ ID NO:25]
m35-dRNA        .......... .......... .......... .......... .......... [SEQ ID NO:19]
m35-fRNA        .......... .......... .......... .......... .......... [SEQ ID NO:21]
m35-aRNA        AGGATACCAG AGTGGGAAGG GGGGCGGGGA AACAGAAGAC ACTAGACTCT [SEQ ID NO:15]
m35c1RNA        .......... .......... .......... .......... .......... [SEQ ID NO:17]

                2051                                                 2100
m35-hRNA        CACAGTCTTC TTCTTGAGTG GGGCTCTGAC ACCCACAGCC AAATTCACAA
m35ge-RNA       .......... .......... .......... .......... ..........
m35-dRNA        .......... .......... .......... .......... ..........
m35-fRNA        .......... .......... .......... .......... ..........
m35-aRNA        AGTTACTAGA GGAGAATACT AAATCCAGTA CTGTTGAGTG AGGGAAAGAT
m35c1RNA        .......... .......... .......... .......... ..........

                2101                                                 2150
m35-hRNA        CTAACATGGG TGTTCTCCAA CTTTGTGGAA GAAGAGTCCC CAGGTTAGCA
m35ge-RNA       .......... .......... .......... .......... ..........
m35-dRNA        .......... .......... .......... .......... ..........
m35-fRNA        .......... .......... .......... .......... ..........
m35-aRNA        GGACTGGCTC AACTATTTTT TTTCCTTTTT CTATTTTGTT TTGAAAAGTA
m35c1RNA        .......... .......... .......... .......... ..........
```

Figure 5 (continued)

```
          2151                                                2200
m35-hRNA  TCTTCTCAGT GATGACATGT GTTGGACTCT AGTGAGCTTG CCTCTTGTTA [SEQ ID NO:23]
m35ge-RNA ..........  ..........  ..........  ..........  .......... [SEQ ID NO:25]
m35-dRNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:19]
m35-fRNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:21]
m35-aRNA  AGATGTTGGG AAGGGAGGTG TTCAGAATAT AAAACAGAAA TGTAGGGAGA [SEQ ID NO:15]
m35c1RNA  ..........  ..........  ..........  ..........  .......... [SEQ ID NO:17]

          2201                                                2250
m35-hRNA  AGAGGATGGT TTTCATTTGC TTCAGGGGTA TACCTGCCAG TCAGTCAGCC
m35ge-RNA ..........  ..........  ..........  ..........  ..........
m35-dRNA  ..........  ..........  ..........  ..........  ..........
m35-fRNA  ..........  ..........  ..........  ..........  ..........
m35-aRNA  ATACAAAAGA AGTGCTGTTT CTAGGATCAT ATATAACCTC ACCAAACCTT
m35c1RNA  ..........  ..........  ..........  ..........  ..........

          2251                                                2300
m35-hRNA  ACATTCCCAC TCATGCTCAG ACCAACAATC ATGGTTAAAC TCTGTGGGAC
m35ge-RNA ..........  ..........  ..........  ..........  ..........
m35-dRNA  ..........  ..........  ..........  ..........  ..........
m35-fRNA  ..........  ..........  ..........  ..........  ..........
m35-aRNA  GTTGACGGCT CTGCCTGAGC TTGCAGGACC CCCCTCCCTT CCCCTCCCCT
m35c1RNA  ..........  ..........  ..........  ..........  ..........
```

Figure 5 (continued)

```
            2301                                                  2350
m35-hRNA    ACACACACAC ACACACACAC ACACACACAC ACACACACAC GACATATAAT [SEQ ID NO:23]
m35ge-RNA   .......... .......... .......... .......... .......... [SEQ ID NO:25]
m35-dRNA    .......... .......... .......... .......... .......... [SEQ ID NO:19]
m35-fRNA    .......... .......... .......... .......... .......... [SEQ ID NO:21]
m35-aRNA    TCCAGTATTT GCAGATGCTC CGTTTACAGA GGGGTCCTCT CACCATGCAC [SEQ ID NO:15]
m35c1RNA    .......... .......... .......... .......... .......... [SEQ ID NO:17]

            2351                                                  2400
m35-hRNA    CAGGAGAGGG ACTCATTAGA GCCTGTAGGT CAGGCAGTGG TAGCACATGC
m35ge-RNA   .......... .......... .......... .......... ..........
m35-dRNA    .......... .......... .......... .......... ..........
m35-fRNA    .......... .......... .......... .......... ..........
m35-aRNA    AGCCCACTAC GCATCACACG CTGTCTCGTC ATAAGCATCC CTCCGTGTTC
m35c1RNA    .......... .......... .......... .......... ..........

            2401                                                  2450
m35-hRNA    CTTTAATCTC AACACTCAGG AGGCAGAGGC AGGTGGATTT CTGAGTTCTA
m35ge-RNA   .......... .......... .......... .......... ..........
m35-dRNA    .......... .......... .......... .......... ..........
m35-fRNA    .......... .......... .......... .......... ..........
m35-aRNA    TACGAACTTT GTACAATAAA CTTTCTCAGC TGTGTAGTAT TT........
m35c1RNA    .......... .......... .......... .......... ..........
```

Figure 5 (continued)

```
            2451                                                    2500
m35-hRNA    GGTCAGTCTG CTTTACAGAG TGAGTTCTAG GACTACACAG AGAAATCCAA [SEQ ID NO:23]
m35ge-RNA   .......... .......... .......... .......... .......... [SEQ ID NO:25]
m35-dRNA    .......... .......... .......... .......... .......... [SEQ ID NO:19]
m35-fRNA    .......... .......... .......... .......... .......... [SEQ ID NO:21]
m35-aRNA    .......... .......... .......... .......... .......... [SEQ ID NO:15]
m35c1RNA    .......... .......... .......... .......... .......... [SEQ ID NO:17]

            2501                                                    2550
m35-hRNA    AAAAACAAGG CTACACAGAG AAACCATGTC CTGGGGTAAA AAAGAAAAAG
m35ge-RNA   .......... .......... .......... .......... ..........
m35-dRNA    .......... .......... .......... .......... ..........
m35-fRNA    .......... .......... .......... .......... ..........
m35-aRNA    .......... .......... .......... .......... ..........
m35c1RNA    .......... .......... .......... .......... ..........

            2551
m35-hRNA    AAAA
m35ge-RNA   ....
m35-dRNA    ....
m35-fRNA    ....
m35-aRNA    ....
m35c1RNA    ....
```

Figure 5 (continued)

```
m35eIg-aa  .......... .......... ...GCCTAQD PVTGPEEVSG QEQGSLTVQC [SEQ ID NO:27]
 m35h-aa   .......... MWQFSALLLF FLPGCCTAQD SVTGPEEVSG QEQGSLTVQC [SEQ ID NO:24]
m35ge-aa   .........M HLSLLVPFLF WITGCCTAED PVTGPEEVSG QEQGSLTVQC [SEQ ID NO:26]
 m35f-aa   .......... MRLCAGLLLL CFQGC....L SLTGPGSVSG YVGGSLRVQC [SEQ ID NO:22]
 m35d-aa   .......... MWLSPALLLL SFPGC....L SIQGPALVRG PEQGSVTVQC [SEQ ID NO:20]
 m35c-aa   MTQLASAVWL PTLLLLLLLF WLPGC....V PLHGPSTMTG SVGQSLSVSC [SEQ ID NO:18]
 m35a-aa   .......... ...MRPLVLL WGCLVLPGYE ALKGPKEISG FEGDTVSLRC [SEQ ID NO:16]

           51                                                    100
m35eIg-aa  RYDSGWKDYK KYWCR..GAY WKSCEILVET DASEQLVKEN RVSIRDDQTD
 m35h-aa   RYSSYWKGYK KYWCR..GVP QRSCDILVET DKSEQLVKKN RVSIRDNQRD
m35ge-aa   RYTSGWKDYK KYWCQ..GVP QRSCKTLVET DASEQLVKKN RVSIRDNQRD
 m35f-aa   QYSPSYKGYM KYWCR..GPH DTTCKTIVET DGSEKEKRSG PVSIRDHAAN
 m35d-aa   RYSSRWQTNK KWWCR..GAS WSTCRVLIRS TGSEKETKSG RLSIRDNQKN
 m35c-aa   QYEEKFKTKD KYWCR..GSL KVLCKDIVKT SSSEE.ARSG RVTIRDHPDN
 m35a-aa   TYVEKMKEHR KYWCRQGGIL VSRCGDIVYA NQ.DQEVTRG RMSIRDSPQE

           101                                                   150
m35eIg-aa  FIFTVTMEDL RMSDADIYWC GITKA..... .GTDPMFKVN VNIDP.....
 m35h-aa   FIFTVTMEDL RMSDAGIYWC GITKG..... .GPDPMFKVN VNIDQAPKSS
m35ge-aa   FIFTVTMEDL RMSDAGIYWC GITKV..... .PTMPPITST TTIFTVTTTV
 m35f-aa   STITVIMEDL SEDDAGSYWC KIQTSFIWDS WSRDPSVSVR VNVFPVNSGQ
 m35d-aa   HSFQVTMEML RQNDTDTYWC GIEK...... FGTDRGTRVK VNVYFGHMQT
 m35c-aa   LTFTVTYESL TLEDADTYMC AVDISLFDGS LGFDKYFKIE LSVVPSEDPG
 m35a-aa   LSMTVIMRDL TLKDSGKYWC GIDR...... LGRDESFEVT LIVFPGSSRP
```

Figure 6

```
                151                                                 200
m35eIg-aa  .......... .......... .......... .......... ..........[SEQ ID NO:27]
 m35h-aa   MMTTTATVLK SIQPSA.ENT GKEQVTQSKE VTQSRPHTRS LLSSIYFLL.[SEQ ID NO"24]
m35ge-aa   KETSMFPTLT SYYSDN.GHG GGDSGGGEDG VGDGFLDLSV LLPVISAVL.[SEQ ID NO:26]
 m35f-aa   NLRISTNVMF IF........ .......... ......QLWS LLSSIQFQV.[SEQ ID NO:22]
 m35d-aa   FFSSAATLTP ERAAEMWVKI PCRLLINFPG PLWTAVQTWC LLTCRRGLEA[SEQ ID NO:20]
 m35c-aa   PTLETPVVST SLPTKGPALG SNTEDRREHD YSQG.LRLPA LLSVLALLLF[SEQ ID NO:18]
 m35a-aa   VVWLPLTT.. ........PQ DSRAVASSVS KPSVSIPMVR MMAPVLILLS[SEQ ID NO:16]

                201                                                 250
m35eIg-aa  .......... .......... .......... .......... ..........
 m35h-aa   .MVFVELPLL LSM........ ..LSAVLWVT RPQRCFGRGE NDLVKTHSPV
m35ge-aa   .LLLLLVASL FAWRMVRRQK KDLSLKQPRT SPGSSWKKGS SMSSSGKDHQ
 m35f-aa   .LVFLKLPLF LSMLCAIFWV NRL*...... .......... ..........
 m35d-aa   SLVGAFVGGL MQVPSCSLAV AIFTFVLTLT PPSSQEAHST PSSHSAPVAS
 m35c-aa   LLVGTSLLAW RMFQKRLVKA DRHPELSQNL RQASEQNECQ YVNLQLHTWS
 m35a-aa   LLLAAGLIAF GSHMLRWRKK AWLATETQKN EKVYLETSLP GNGWTTEDST

                251                                                 300
m35eIg-aa  .......... .......... .......... .......... ..........
 m35h-aa   A.......... .......... .......... .......... ..........
m35ge-aa   EEVEYVTMAP FPREEVSYAA LTLAGLGQEP TYGNTGCPIT HVPRTGLEEE
 m35f-aa   .......... .......... .......... .......... ..........
 m35d-aa   KEEMNRLF*. .......... .......... .......... ..........
 m35c-aa   LREEPVLPSQ VEVVEYSTLA LPQEELHYSS VAFNSQRQDS HANGDSLHQP
 m35a-aa   IDLAVTPECL RNLNPSAVPS PETQNLSQST EEEEAARSLD DDKEDVMAPP
```

Figure 6 (continued)

```
          301                   323
m35eIg-aa ..... ..... ...[SEQ ID NO:27]
  m35h-aa ..... ..... ...[SEQ ID NO:24]
 m35ge-aa TTEYSSIRRP LPAAMP*... ...[SEQ ID NO:26]
  m35f-aa ..... ..... ...[SEQ ID NO:22]
  m35d-aa ..... ..... ...[SEQ ID NO:22]
  m35c-aa QDQKAEYSEI QKPRKGLSDL YL*[SEQ ID NO:18]
  m35a-aa PLQMSAEELA FSEFISV*.. ...[SEQ ID NO:16]
```

Figure 6 (continued)

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		Spleen	Thymus	Lymph Node	Kidney	Liver	Heart	Skin	Bone Marrow	Gut	T lympo-cyte EL4	macro-phage RAW	macro-phage J774	mono/macro P388D1	P815	CD11b (G)	CD11b (M)	B cell CD45R	T cell CD3
m35a	BALB/c mouse 2	+	+	+	+	+	+	+	+	+									
	cell lines										---	+++	+++	+++	---	++	-	-	-
m35c	BALB/c mouse 2	+++	+++	+++	+++	+++	+++	+++	+++	+++									
	cell lines										--	+++	+++	+++	+++	++	++	++	++
m35d	BALB/c mouse 2								+++										
	cell lines											+++	+++			+-	++	++	++
m35e	BALB/c mouse 2	+	+	+	+	+	+	+	+++	+++									
	cell lines										—	+++	+++	---	—	-	-	-	-
m35f	BALB/c mouse 2	++	-	--	--	++	--	-	---	—									
	cell lines							-			---	+++	+++	—	---	-	-	-	-
m35g	BALB/c mouse 2	+	+	+	+	+	+	-	+++	—									
	cell lines										+++	+++	+++	+++	+++	-	-	-	-

Figure 7

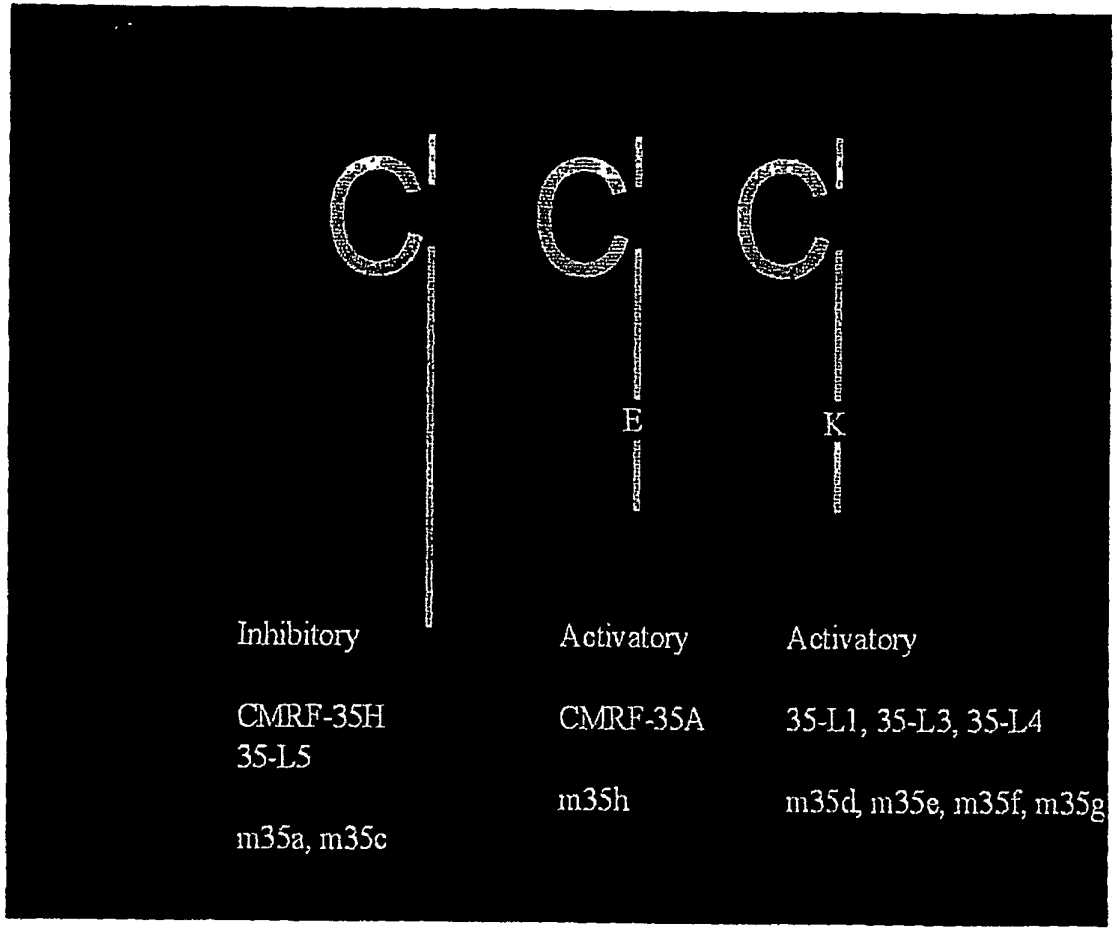


Figure 8

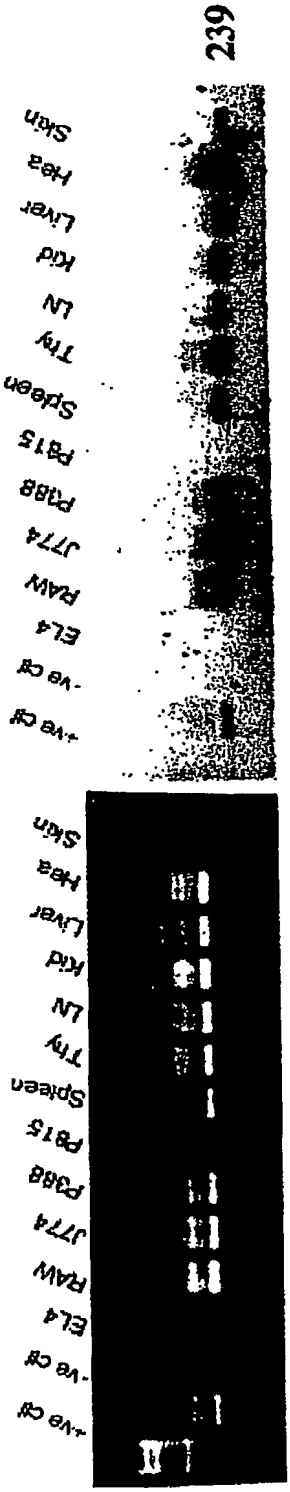


Figure 9A

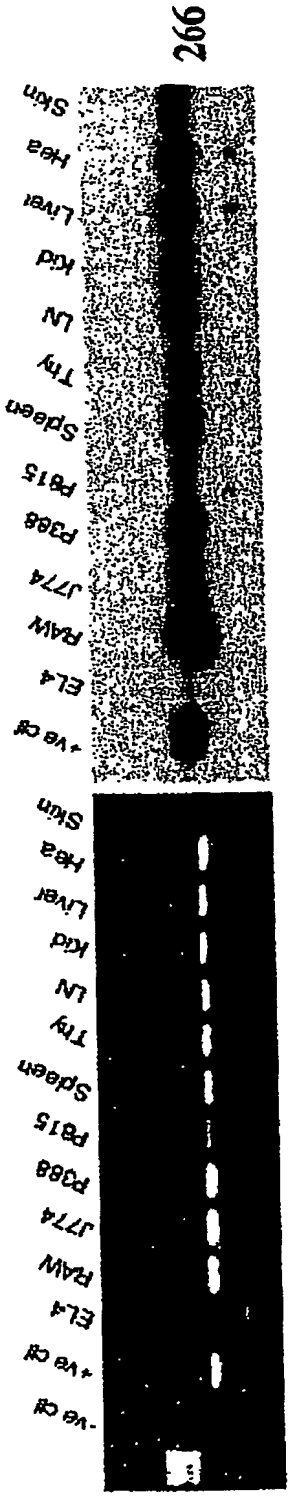


Figure 9B

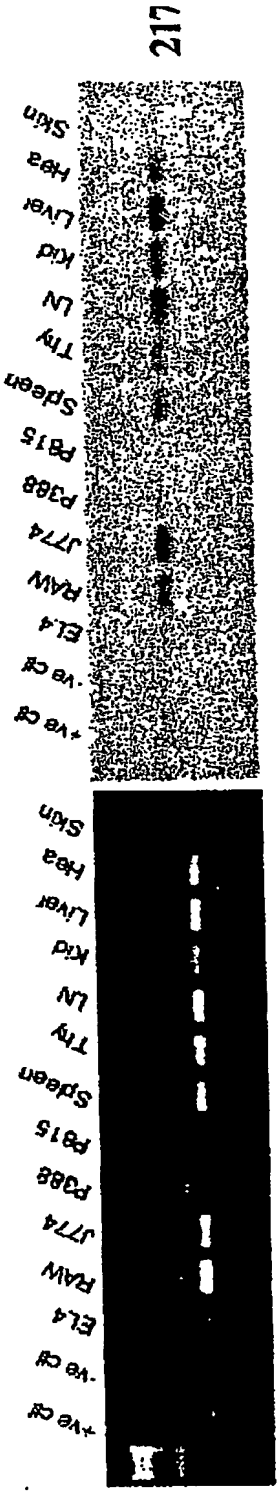


Figure 9C

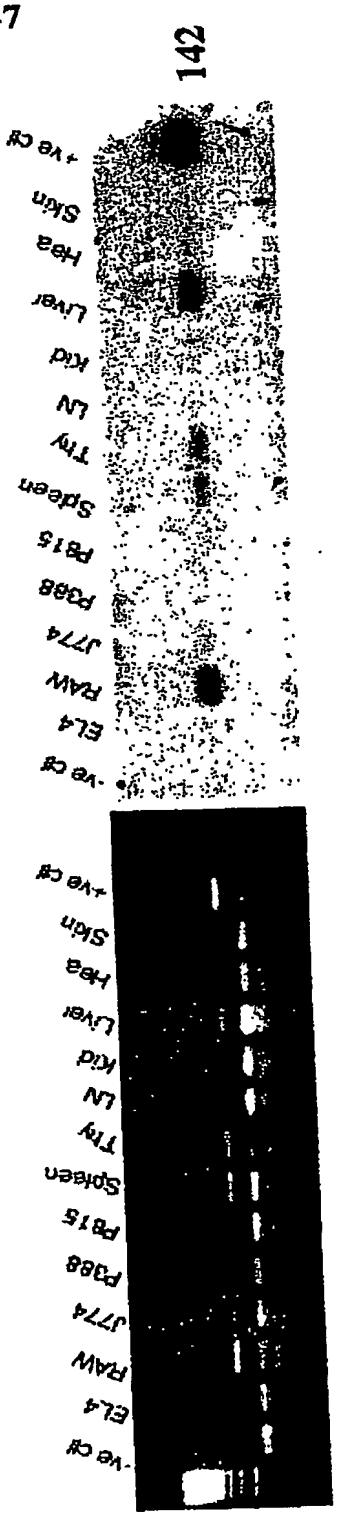


Figure 9D

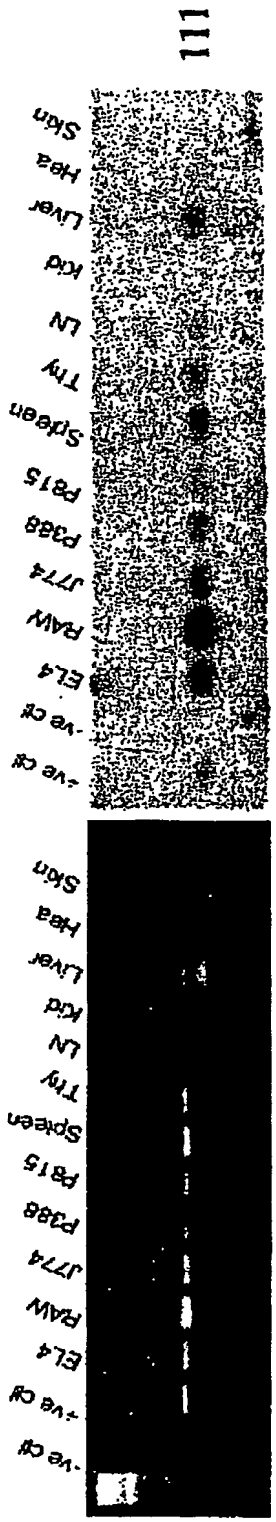
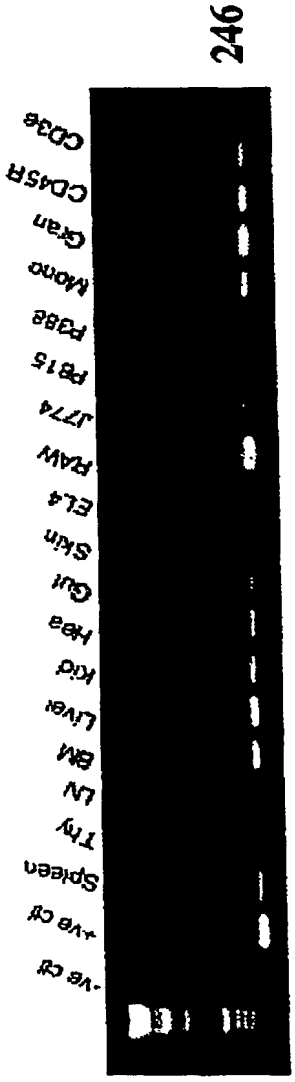


Figure 9E



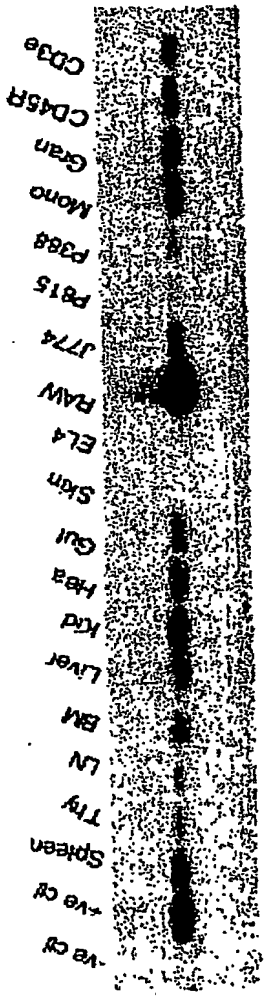


Figure 9F

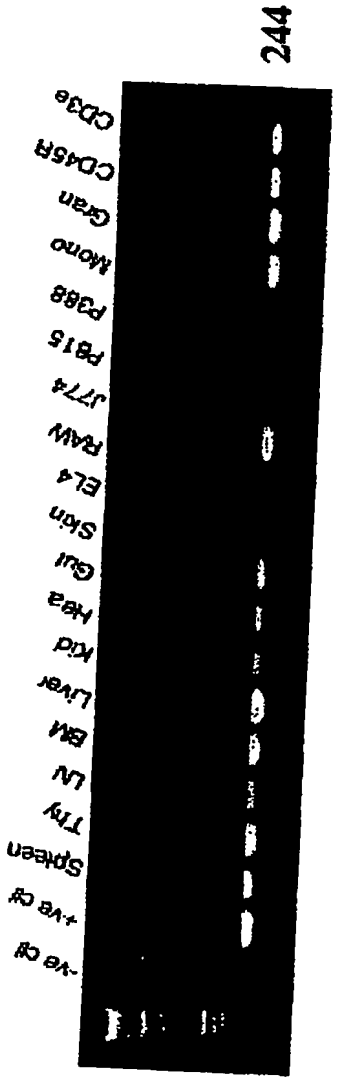


Figure 9G

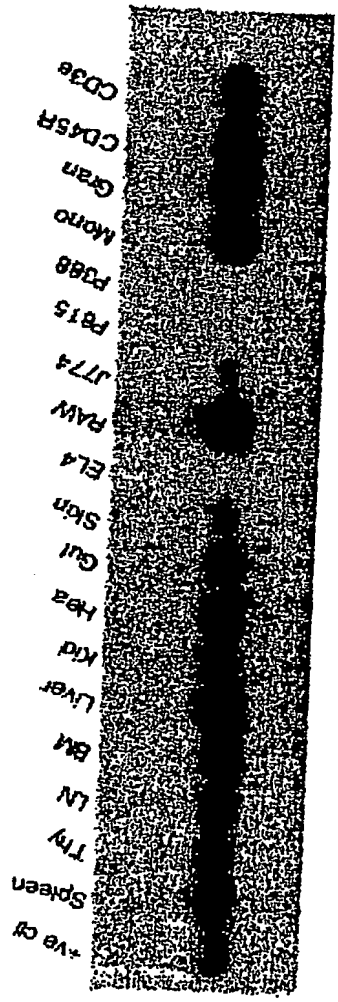


Figure 9H

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